Healthy Ageing and Advanced Dementia

Promoting Medical Decision-Making in Various Decision-Makers

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Abstract

In advanced dementia, patients commonly experience burdensome medical interventions that may be of limited clinical benefit and do not promote a good quality of life and death. This thesis objective is to better understand and improve medical decision-making in advanced dementia among physicians, relatives of persons with dementia, and professional guardians, as well as to examine associations between decision-making supports and health outcomes in both decision-makers and patients. To this end, three studies were conducted. Findings revealed that having had a goals of care discussion with a physician helped proxies perceive that the resident may have a poor prognosis, which was in turn associated with the receipt of fewer burdensome interventions. Decision support tools reduced decisional conflict, increased knowledge, and shifted preferences in favor of foregoing antibiotics in advanced dementia among various decision-makers. Lastly, proxies were more likely to consider assisted dying in advanced dementia than physicians, and about half of the participants in both groups reported continuous deep sedation to be an appropriate option for this population. This thesis addresses many global public health priority topics such as dementia and palliative care, and has significant implications for the improvement of medical decision-making in advanced dementia.

Zusammenfassung

Patienten mit fortgeschrittener Demenz werden häufig belastenden medizinischen Interventionen unterzogen, ohne dass dabei eine Verbesserung der Lebensqualität zu erwarten ist. Ziel dieser Dissertationsarbeit ist es, medizinische Entscheidungsfindungen von Ärzten, Angehörigen, und Berufsbeiständen im Kontext von fortgeschrittener Demenz zu verstehen und verbessern, sowie den Zusammenhang zwischen Entscheidungshilfen und gesundheitlichen Outcomes von Entscheidungsträgern und Patienten zu untersuchen. Zu diesem Zweck, wurden drei Studien durchgeführt. Die Ergebnisse zeigten, dass Angehörige, die die Behandlungsziele mit einem Arzt besprochen hatten, dazu neigten die Prognose des Bewohners als schlechter wahrzunehmen. Diese Wahrnehmung war mit einer geringeren Durchführung von belastenden Interventionen verbunden. Entscheidungshilfen in diversen Entscheidungsträgergruppen führten zu reduziertem Entscheidungskonflikt, erhöhtem Wissen, und gesteigerten Präferenzen für den Antibiotika-Verzicht bei fortgeschrittener Demenz. Stellvertreter im Vergleich zu Ärzten neigten dazu Sterbehilfe für Demenzpatienten zu befürworten, und etwa die Hälfte der Studienteilnehmer in beiden Gruppen hielt kontinuierliche tiefe Sedierung für eine geeignete Option für diese Population. Diese Dissertationsarbeit befasst sich mit globalen Gesundheitsthemen wie Demenz und Palliative Pflege und hat erhebliche Implikationen für die Verbesserung von medizinischer Entscheidungsfindung bei fortgeschrittener Demenz.

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1. Introduction

Dementia afflicts more than 50 million people worldwide and is one of the most common causes of death in Switzerland (Federal Statistical Office FSO, 2017; World Health Organization, 2015a). In advanced dementia, patients have profound deficits and experience repeated complications (Hendriks, Smalbrugge, Hertogh, & van der Steen, 2014; Mitchell et al., 2009). As a result, these patients commonly experience burdensome interventions that may be of limited benefit and do not promote a good quality of life (Gozalo et al., 2011; Meier, Ahronheim, Morris, Baskin-Lyons, & Morrison, 2001; Mitchell et al., 2009; Mitchell, Morris, Park, & Fries, 2004c; Mitchell et al., 2014; Mitchell, Teno, Roy, Kabumoto, & Mor, 2003; Morrison & Siu, 2000b).

Because of the impaired decisional capacity that accompanies advanced dementia, legally authorized decision-makers, mostly relatives but also professional guardians, along with physicians are responsible for medical decision-making (A. B. Cohen, Wright, Cooney, & Fried, 2015; Givens, Kiely, Carey, & Mitchell, 2009). However, these decision-makers report inadequate decisional support and burdensome decision-making (Engel, Kiely, & Mitchell, 2006; Givens et al., 2009; Pautex et al., 2013; You et al., 2015). Consequently, they frequently make treatment decisions on behalf of the patient that do not align with the patient's goals of care (D'Agata & Mitchell, 2008; Mitchell et al., 2009; 2014; 2017). Despite substantial progress in advanced dementia research, our understanding of medical decision-making and its impact on outcomes that enable healthy ageing of both decision-makers and patients is limited (Mitchell et al., 2012; van der Steen, Sternberg, & Volicer, 2017b; World Health Organization, 2017).

The purpose of this thesis is to better understand and promote medical decision-making in advanced dementia among physicians, relatives of persons with dementia, and professional guardians, and to examine associations between decision-making supports and health outcomes in both decision-makers and patients. To this end, the first chapter will apply the concept of *Healthy Ageing* to terminal diseases such as dementia and motivate hypotheses in the more specific context of advanced dementia. Next, I will present treatment decisions for common complications in advanced dementia, discuss the use of controversial practices (e.g., assisted dying), and highlight challenges that may arise when making decisions on behalf of these patients. After reviewing the existing research on the promotion of high-quality decision-making and care, I will present three studies that were conducted for this thesis and contribute to that literature. While studies 1 and 2 provide novel insights about the role of different forms of support in improving decision-making and care, study 3 explores perceptions about controversial practices in advanced dementia. In the third and last chapter, I will summarize these three studies, discuss their findings, and present their strengths and limitations. Lastly, I will conclude by illustrating the implications of this work for future research and for the management of advanced dementia.

1.1. Healthy Ageing

Healthy Ageing is an intergenerational and intercultural common life-goal. Every human being wishes to age as healthy as possible. But what does *healthy ageing* mean in the context of chronic and terminal illnesses such as Alzheimer's disease and other dementias?

The concept of *Healthy Ageing* refers to the maintenance of functional quality of life even in the face of disease (Martin, Jäncke, & Röcke, 2012a; Martin, Schneider, Eicher, & Moor, 2012b; Scholz, König, Eicher, & Martin, 2015; World Health Organization, 2015b).

Individuals are no longer categorized into *healthy* versus *unhealthy*, but are instead thought to be situated on a continuum of functionality going from less functional to fully functional. Individuals are thus *functional* when their health is *maintained* or *stabilized* as suggested by the the *f*unctional Quality of Life model (*f*QoL) (Martin, Schneider, Eicher, & Moor, 2012b). Further research has examined the stabilization of health as an indicator of *well-being* (Martin, Jäncke, & Röcke, 2012a; 2016; Scholz et al., 2015). In this context, the homeostasis of health is a focal goal throughout every individual's lifespan (Martin, Jäncke, & Röcke, 2012a; Scholz et al., 2015; Wilkening & Martin, 2003).

In line with this research, the World Health Organization (WHO) has defined *Healthy Ageing* as *the process of developing and maintaining the functional ability that enables well-being in older age* (page 28; World Health Organization, 2015b). This concept has been more specifically defined in a framework that suggests three domains influencing an individual's ability to be functional: 1. intrinsic capacities (physical and mental abilities or impairments); 2. functional ability (health attributes enabling an individual to act as desired); and 3. environment (micro- and macro-level). An individual's ability to function depends on the interaction between their intrinsic capacities (e.g., personal and health characteristics) and their environment. Resources from the environment may include people and their relationships (e.g., caring family members or open health care provider staff), but also health policies (e.g., guidelines on palliative care in dementia), and supporting systems or services (e.g., specialized dementia care unit). Successful activation of adequate resources from these domains can enable *healthy ageing* despite a chronic and terminal illness.

Most individuals successfully manage to maintain high levels of functioning in older age,(Martin, Jäncke, & Röcke, 2012a) but maintain functioning is more challenging for those

affected by chronic and terminal illnesses such as dementia (Scholz et al., 2015). In advanced dementia, the intrinsic capacities of the patient are severely impaired,(Mitchell et al., 2009) and there is currently no therapy to cure dementia and thus stabilize functions. However, stabilization may be achieved using palliative medicine to control symptoms and increase comfort (van der Steen et al., 2014). Patients with advanced dementia are unable to communicate needs or ask for support because of the cognitive impairments that accompany the condition. Consequently, the patient's environment (e.g., health care system, clinical guidance, dementia policies, or legal authorized decision-makers) is responsible for anticipating, recognizing, and fulfilling the patient's needs to enable *well-being with dementia* and to do so *until death*.

It is challenging to determine the specific elements that need to be adjusted in order to maintain functioning in old age for a given individual (Martin, Jäncke, & Röcke, 2012a). In advanced dementia, despite increasingly dementia-friendly societies, progress in palliative medicine, and caring families, most patients still experience a poor quality of life and death.

1.2. Advanced Dementia

Dementia is a terminal disease defined by neuropathologic changes or biomarkers, which cause memory and other cognitive abilities to gradually worsen, leading to confused behavior (Jack et al., 2018; World Health Organization, 2017). As a result, the person's ability to carry out complex but essential tasks in daily life is compromised. Dementia is an umbrella term that covers a wide range of diseases, the most common forms are Alzheimer disease, which contributes to 60-70% of cases, vascular dementia, dementia with Lewy bodies, and others defined as frontotemporal dementia (World Health Organization, 2015a).

1.2.1. Epidemiology

More than 50 million people worldwide are affected by dementia, a number that roughly corresponds to the population of Spain (Alzheimer's Disease International, 2013). With an ageing global demographic, this number is expected to increase by 50% by 2030, and even reach 136 million by 2050 (World Health Organization, 2015a). In Switzerland, dementia afflicts about 133 thousands people and is one of the most common causes of death (Alzheimer Europe, 2014). Every three seconds someone in the world begin to develop dementia (Alzheimer's Disease International, 2015). The average life expectancy from the onset of dementia until death is approximately five years (Xie, Brayne, Matthews, Medical Research Council, 2008). One in three people over the age of 65 die with dementia (Brayne, Gao, Dewey, Matthews, Medical Research Council, 2006). Most people with dementia die in nursing homes (in the United Sates, 67%; the Netherlands, 92%; Belgium, 66%; and England, 60%), making those facilities key settings for end-of-life care (Houttekier et al., 2010; Mitchell, Teno, Miller, & Mor, 2005).

Given the increasing prevalence of dementia, the burden places on current and future global public health is enormous and growing. In 2015 associated global costs were estimated to be as high as USD 818 billion annually (or CHF 767 billion) and included direct medical, social care, and informal care costs (World Health Organization, 2017). The World Health Organization (WHO) anticipates this cost to more than double by 2030, which could have dramatic consequences on a variety of social and health services including long-term care systems such as nursing homes. Costs vary according to dementia severity; the costs associated with advanced dementia are more than twice as high as those associated with mild dementia (Quentin, Riedel-Heller, Luppa, Rudolph, & König, 2010).

In light of the severity of the situation and its dramatic forecasts, the WHO has published a global action plan on the public health response to dementia for the time period of 2017 through 2025 and simultaneously established a global dementia observatory (World Health Organization, 2016; 2017). The action plan lists several action areas of high priority, and this thesis addresses action areas on treatments, medical decision-making, and support (see action areas 4, 5, and 7; World Health Organization, 2017). The Global Dementia Observatory is a web-based platform that aims to track global progress related to dementia in approximately 50 countries (World Health Organization, 2016). The platform will enable authorities including health care providers and researchers to easily access and share documents such as global reports, policies, and guidelines on dementia care. While the observatory is positioned to be an important tool in coordinating and ensuring dementia-friendly care at a global scale, it also implies a need for evidence-based, standardized guidelines that form the basis of such coordination.

Dementia is a terminal condition and, in the face of an ageing population, more and more people are expected to live and die with dementia. The societal burden of advanced dementia is substantial and growing. In response to this alarming situation, the WHO has recently published an action plan on dementia and developed the global dementia observatory.

1.2.2. Clinical Course

Advanced dementia is characterized by a prolonged trajectory of severe disability, associated with major impairments in the last year of life (Hendriks et al., 2014; Mitchell et al., 2009). Reisberg and colleagues have developed the Global Deterioration Scale for the assessment of primary degenerative dementia (Reisberg, Ferris, de Leon, & Crook, 1982).

The scale states advanced dementia to be defined by an inability to recognize family members, an inability to speak more than five words, by being bedbound, incontinent of urine and stool, and totally dependent in activities of daily living. Although this definition has been put forward in 1982, it has not been until a quarter-century later that the clinical course of patients with advanced dementia has been well described.

The Choices, Attitudes, and Strategies for Care of Advanced Dementia at the End-of-Life (CASCADE) study constitutes the first description of the clinical course of advanced dementia (Mitchell et al., 2009). This study followed 323 nursing home residents with advanced dementia over a period of 18 months and was conducted in 22 nursing home facilities of the greater Boston area. Over the 18-month study period, 55% of residents died, 86% developed a feeding problem, 41% had pneumonia, and 53% had a febrile episode. These findings revealed that advanced dementia is characterized by a high mortality rate, and that complications such as infections, feeding problems, fever, dehydration, or other illnesses should be expected. Not only is it common for complications to occur at all but they are also expected to re-occur. Repeated pneumonia episodes are typical of the end-stage of the disease.

As a consequence of the trajectory of severe disability, patients commonly experience significant distress symptoms (Hendriks et al., 2014; Mitchell et al., 2009; van der Maaden, van der Steen, de Vet, Hertogh, & Koopmans, 2016; van der Steen, Pasman, Ribbe, van der Wal, & Onwuteaka-Philipsen, 2009b). In CASCADE, distress symptoms observed among the 323 residents during the 18-month study period included agitation (54%), dyspnea (46%), aspiration (41%), pressure ulcers (39%) and pain (39%) (Mitchell et al., 2009). These

symptoms frequently increase in the last days of life (Hendriks et al., 2014; van der Maaden et al., 2016).

This description of the clinical course of advanced dementia has been cross-validated in many other countries, revealing similar trajectories of disability and high mortality rate in advanced dementia (Hendriks et al., 2016; Mitchell et al., 2009; van der Steen, Pasman, Ribbe, van der Wal, & Onwuteaka-Philipsen, 2009b; Vandervoort et al., 2013). However, evidence about the clinical course of Swiss patients is lacking. The Zurich Life and Death with Advanced Dementia (ZULIDAD) study will be the first to describe the clinical course and quality of life and dying of residents with advanced dementia in Switzerland (Eicher et al., 2016). ZULIDAD is a prospective cohort study conducted in 11 nursing homes in the greater Zurich area that followed triads of residents with advanced dementia, their relatives, and primary nurses. The data collection was recently completed. Forthcoming findings from this study may provide novel insights about the nursing situation and needs of those affected by advanced dementia in Switzerland.

1.2.3. Treatments for Common Complications

Clinical complications experienced by patients with advanced dementia are commonly accompanied by distress symptoms at the end of life (Hendriks et al., 2014; Mitchell et al., 2009; van der Maaden et al., 2016; van der Steen, Pasman, Ribbe, van der Wal, & Onwuteaka-Philipsen, 2009b). Treatment decisions thus have to be made on behalf of the patient to potentially cure the underlying complication, reduce distress symptoms and promote comfort.

About two-thirds of people with advanced dementia die from pneumonia (Osler, 1898; Thomas, Starr, & Whalley, 1997; van der Steen et al., 2006; van der Steen, Ooms, van

der Wal, & Ribbe, 2002). Decisions related to the use antibiotics are the most common end-of-life decisions in this population followed by decisions such as those relating to the use of parenteral therapy, tube feeding, or hospitalization (Di Giulio et al., 2008; Hendriks et al., 2016; Mitchell et al., 2009). Of the 323 residents with advanced dementia in the CASCADE study, 34% received parenteral therapy, 17% were hospitalized, 10% were taken to the emergency room, and 8% were tube fed. Of these 32, 41% underwent burdensome interventions in their last three months of life (Mitchell et al., 2009). Research has shown that these interventions may be of limited clinical benefit and may not promote comfort-focused care (Gozalo et al., 2011; Meier et al., 2001; Mitchell et al., 2003; 2009; 2014; Mitchell, Morris, Park, & Fries, 2004c; Morrison & Siu, 2000b; van der Steen et al., 2014).

The use of antibiotics in patients with advanced dementia illustrates well the uncertainty about the benefit-to-harm ratio of most curative treatments in this frail and dying population. The Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia (SPREAD) investigated antimicrobial exposure in 363 residents with advanced dementia in 35 nursing home facilities of the greater Boston area over 12 months (Mitchell et al., 2014; Mitchell, Shaffer, Kiely, Givens, & D'Agata, 2013). Among 496 suspected infections in these residents, 72% were treated with antimicrobials. Of these, 56% were treated inappropriately as there was inadequate clinical evidence of a bacterial infection. Over the course of the study, 67% of the residents became colonized at some point with antibiotic resistant bacteria, and exposure to an antibiotic was the strongest risk factor for bacterial colonization. Patients commonly receive antibiotics during their last days of life and often in addition to invasive rehydration therapy (D'Agata & Mitchell, 2008; Hendriks et al., 2014; van der Steen et al., 2017a).

Antimicrobials may effectively treat infections, but they are frequently inappropriate in advanced dementia (Mitchell et al., 2014). First, the diagnosis of a suspected infection requires burdensome procedures. For example, to diagnose a respiratory tract infection the already frail resident is transferred to the hospital to undergo a chest X-ray test. Hospitalization can be traumatic for both patients and family members, and is associated with poor outcomes in these frail patients (Dewing & Dijk, 2016; Epstein-Lubow et al., 2012). Second, antimicrobials may be used in the absence of infection because antibiotics are frequently administered without meeting minimal criteria for administration (D'Agata, Loeb, & Mitchell, 2013). Third, the administration of the treatment itself often requires an intensive procedure that can cause discomfort for the frail patient. Because of swallowing difficulties that accompany advanced dementia, antibiotics are commonly given via infusion, which require the placement of a needle in the vein (D'Agata & Mitchell, 2008). Fourth, significant side effects of antibiotics add to the aforementioned aspects, further suggesting that potential clinical benefit may be outweighed by adverse consequences. Antimicrobials can provoke diarrhea, allergic reactions (e.g., skin rashes), nausea, or vomiting. The benefit-to-harm ratio of antimicrobial use on survival and comfort in advanced dementia remains unclear (Givens, Jones, Shaffer, Kiely, & Mitchell, 2010; van der Steen, Lane, Kowall, Knol, & Volicer, 2012). Lastly, most treatments are prescribed without taking into account the high likelihood of the complication re-occuring and in unawareness of the terminal condition of these dying patients (Mitchell et al., 2009; 2014; Mitchell, Kiely, & Hamel, 2004a; van der Steen, Onwuteaka-Philipsen, Knol, Ribbe, & Deliens, 2013).

Another major issue of the extensive misuse of antibiotics is the spread of Multi-Drug-Resistant-Organisms (MDROs). Antimicrobial overuse may result in the development of MDROs, which are bacteria that have become ‘resistant’ to many commonly used

antibiotics. In SPREAD, most treatment decisions were inappropriate and antibiotic resistant bacteria were present in most residents with advanced dementia (Mitchell et al., 2014). These bacteria may cause antibiotics to not work when really needed and provoke other infections which may cause death or prolonged illnesses, leading to long hospital stays, isolation measures, and increased costs (Kronenberg, Zanetti, Piffaretti, & Mühlemann, 2008; World Health Organization, 2014a). Bacteria can be transmitted from individual to individual. MDROs thus affect not only human health, but they also result in negative public health outcomes and tremendous, preventable costs for the health-care sector (World Health Organization, 2014a). Therefore, the reduction of antibiotic resistant infections is a priority of the World Health Organization and a worldwide concern (Ho, Tambyah, & Paterson, 2010; World Health Organization, 2014b).

In this context, to control distressing symptoms and promote comfort in frail patients with advanced dementia other treatments than antibiotics may be considered. *Palliative Care* focuses on relieving symptoms, pain, and mental distress and recent guidelines suggest prioritizing this approach among patients with advanced dementia (Swiss Academy of Medical Sciences, 2017; van der Steen et al., 2014). Pain, agitation, and shortness of breath are symptoms that may be effectively treated with standard palliative medications (Hendriks et al., 2014; Mitchell et al., 2009). A study in the Netherlands investigated symptoms and treatments and their associations with quality of life in the last 7 days of life among 330 nursing home residents with advanced dementia (Hendriks et al., 2014). Their data showed that residents received opiods (77%), anxiolytic or hypnotic medication (57%) and palliative sedation (21%) when death was imminent. Not receiving these palliative treatments was associated with a lower quality of life in these patients.

Taken together, residents with advanced dementia commonly receive potentially aggressive interventions that may be of little clinical benefit and may not promote comfort at the end-of-life. In the specific case of antibiotic treatments, there is a clear need to reduce the amount of antibiotics prescribed to residents with advanced dementia, which would improve comfort in these residents and contribute to mitigating the public health threat of MDROs. Palliative care should be prioritized to relieve symptoms and improve the quality of life of these frail patients.

1.2.4. Controversial End-of-Life Practices

Advances in medicine and palliative medicine, in particular, have enabled considerable improvement of the health and life of patients with advanced dementia (Kavalieratos et al., 2016; van der Steen et al., 2014). However, certain contexts and situations may require considering the use of assisted dying and continuous deep sedation until death, which are controversial end-of-life practices.

In the fear of an impoverished existence with advanced dementia, patients with early onset dementia and remaining decisional capacity may wish to request physician-assisted suicide (Diehl-Schmid et al., 2017). Physician-assisted suicide refers to self-administration of lethal drugs that are provided by a physician (Radbruch et al., 2016). This procedure thus requires that the recipient is capable of maintaining and acting on that decision. This practice is legal in only a few states in the United States and a limited number of countries, including Switzerland (E. J. Emanuel, Onwuteaka-Philipsen, Urwin, & Cohen, 2016; Li et al., 2017). In 2014, 742 cases of physician-assisted suicide were registered in Switzerland and, of these 6 (0.8%) concerned persons with early-onset dementia capable of decision-making (Federal Statistical Office FSO, 2016). Patients with advanced dementia, however, cannot make such a

request because they are no longer capable of decision-making. In this case euthanasia may be performed, meaning that the physician administers the drugs that cause the person to die (Radbruch et al., 2016). The Netherlands, Belgium, and Luxembourg allow euthanasia for patients with advanced dementia under certain conditions and it must be explicitly requested in an advanced euthanasia directive (Neil, 2016). Following legalization, the proportion of Belgian individuals with a psychiatric disorder or dementia requesting euthanasia has increased from 0.5%, in 2002, to 3.0%, in 2013 (Dierickx, Deliens, Cohen, & Chambaere, 2017). In line with this increase, the views toward assisted dying in dementia seem more accepting over time, although physicians seem more opposed than proxies (Bolt, Snijdewind, Willems, van der Heide, & Onwuteaka-Philipsen, 2015; Kouwenhoven et al., 2015; Rurup, Onwuteaka-Philipsen, Pasman, Ribbe, & van der Wal, 2006; Tomlinson & Stott, 2014; Tomlinson, Spector, Nurock, & Stott, 2015).

Another controversial practice in advanced dementia is continuous deep sedation until death, which is an intensive palliative therapy used as a last resort when all alternative options have failed to alleviate the patient's suffering (Miccinesi et al., 2006; Ziegler, Schmid, Bopp, Bosshard, & Puhan, 2018). Continuous deep sedation uses medications, administered until death with the aim of lowering the level of consciousness and relieving refractory symptoms of patients with a life expectancy of less than two weeks (Cherny, Radbruch, The Board of the European Association for Palliative Care, 2009). This practice has been commonly used in advanced cancer patients who experience extreme physical suffering in their last weeks (McCarthy, Phillips, Zhong, Drews, & Lynn, 2000; Miccinesi et al., 2006; Teunissen et al., 2007). Two studies suggest that this practice may also be used among advanced dementia patients, but there is no direct evidence on its appropriateness for this population (Anquinet et al., 2013; Hendriks et al., 2014).

Assisted dying and continuous deep sedation are controversial end-of-life practices in advanced dementia. Gaining deeper insights on the use of and perceptions about these practices would inform whether they should be seen as valid options in advanced dementia.

1.3. Implications for Medical Decision-Making

Advanced dementia is a terminal condition characterized by a prolonged trajectory of severe disability (Hendriks et al., 2014; Mitchell et al., 2009). Consequently, decisions about the use of treatments are frequent and, in a minority of cases, decisions may also concern controversial end-of-life practices such as assisted dying or continuous deep sedation.

1.3.1. Decision-Makers

Because of the impaired judgment that accompanies advanced dementia, and in the absence of a patient decree, medical decision-making is delegated to legally authorized representatives. Representatives are most often relatives of the person with advanced dementia (Givens et al., 2009). In the absence of relatives, however, professional guardians are appointed by a court and serve as designated, legally authorized representatives (A. B. Cohen et al., 2015). These representatives, along with health care providers, physicians but also nurses, are responsible for medical decision-making on behalf of the patient. Treatment decisions are guided by the patients' care preferences as specified in advanced directives or as perceived by their proxies. Health care providers give their medical expertise based on the patients' best interest. However, research has shown that most decisions made by these decision-makers do not align with the patient's goals of care (D'Agata & Mitchell, 2008; Mitchell et al., 2009; 2014; 2017).

1.3.2. Burdensome Decision-Making

It can be challenging to make medical decisions on behalf of a patient who is incapable of making decisions. While data on the experience of professional guardians making choices about end-of-life care is lacking, most relatives and physicians report burdensome decision-making due to uncertainty about patient's preferences, lacking medical information, and challenging communication about end-of-life care (Engel et al., 2006; Givens et al., 2009; Pautex et al., 2013; You et al., 2015).

Advance directives can provide information about the patient's preferences, but prior research has shown that they are rarely being used in this population (Mitchell et al., 2012; Mitchell, Teno, Intrator, Feng, & Mor, 2007; Tjia, Dharmawardene, & Givens, 2018). A large study conducted in five states of the United States found that 61% of all 44,433 residents with advanced dementia had an advanced directive, and only 5% had specific directives regarding medication restrictions (Tjia et al., 2018). These findings suggest that four in ten residents with dementia lack any advanced directive and when it comes to decisions about medication almost none possessed any written recommendations. In the absence of an advance directive, treatment decisions are guided by the proxy's perceptions of the patient's care preferences. However, their perceptions may be inaccurate and even if there is a written request, the patient's preferences might have changed over time (E. J. Emanuel, Fairclough, & Emanuel, 2000; Harrison Dening, King, Jones, Vickestaff, & Sampson, 2016).

As will be further discussed in the last chapter of this thesis, there are key aspects of dementia and treatment options that decision-makers need to be made aware of in order to ensure informed treatment decisions. The following fundamental medical information should be discussed and understood: 1. terminal condition of dementia; 2. expected re-occurence of

complications (e.g., repeated pneumonia episodes); 3. benefit-to-harm ratio related to treatment administration; 4. benefit-to-harm ratio related to treatment effects; and 5. alternatives to treatments. However, most family proxies are unaware of the terminal nature of advanced dementia and the poor prognosis (Mitchell, Kiely, & Hamel, 2004a). Most decisions about the use of antibiotics are made without taking into account the probability of the pneumonia episodes reoccurring (Mitchell et al., 2014). The benefit-to-harm ratio of treatments may not always be discussed, as it was the case in one-third of decisions about the use of feeding tubes in advanced dementia patients (Teno et al., 2011). Without clear information on benefits and harms of treatments, proxies may perceive decisions not to treat more difficult than decisions to treat and therefore prefer more aggressive treatments (Rabins, Hicks, & Black, 2011).

Communication about end-of-life decisions is difficult for all decision-makers involved. Despite their primary role in decision-making, relatives recall involvement in only about 39% of treatment choices (Givens et al., 2009; 2015). When involved, relatives report high dissatisfaction with decision-making due to lack of counseling and support by health care providers; about half spent less than 15 minutes discussing goals of care (Engel et al., 2006; Givens et al., 2009; Givens, Lopez, Mazor, & Mitchell, 2012). Relatives may have difficulties coping with the situation, discordant opinions with other family members about the 'right' decision, and may be overwhelmed by the turnover of different physicians (Vig, Starks, Taylor, Hopley, & Fryer-Edwards, 2007). Physicians, on the other hand, report challenging end-of-life communication with families due to difficulty accepting a poor prognosis, understanding benefit and harms of treatments, and due to disagreement about goals of care (You et al., 2015). The poor quality of communication may also be reflected in frequent disagreements on the content of these conversations (D. B. White et al., 2016a).

Decision-makers are influenced by their background and personal characteristics, such as coping strategies (Hinkka et al., 2002; Vig et al., 2007).

Consequently, family proxies and physicians of advanced dementia patients experience high dissatisfaction with end-of-life decisions (Givens et al., 2012; Pautex et al., 2013). Uninformed treatment decisions are frequent and may result in poor outcomes for the decision-maker, but also in subsequent over- or undertreatment of the patient (Mitchell et al., 2009; 2014; 2017). Attention to and support for decision-making is needed to ensure that the decisions made on behalf of the patient with advanced dementia are in line with the patient's goals of care are.

1.4. Promoting High-Quality Medical Decision-Making

High-quality decision-making is essential to high-quality care. Measuring the quality of medical decision-making is complex given the patients' inability to take part in decision-making or communicate whether a decision was appropriate.

Delivering goal-directed care (i.e., making appropriate treatment decisions) requires an understanding of the patient's preferences and the set of available treatment options (Mitchell et al., 2017; Rangel, Camerer, & Montague, 2008; van der Steen et al., 2014). A well-established, neuroeconomic framework to formalize decision-making suggests that any appropriate decision is the result of having sufficient knowledge of the range of feasible actions that are subsequently weighted according to their expected values allowing the most desirable option to be selected (Rangel et al., 2008). Outcomes associated with the selection are evaluated ex post to update the weights assigned to the corresponding options. Given the lack of counseling and unawareness about treatment options, proxies have insufficient knowledge and are frequently led to choose more aggressive treatments per default (Rabins et

al., 2011). As a result, they may not be satisfied with their decision and the subsequently observed negative outcomes. Applying the aforementioned decision-making model to decisions that are made on behalf of others, decisional support may promote high-quality decision-making by providing additional choice options. Moreover, it might do so by enabling those preferences (or decision weights) to be incorporated that would otherwise only be part of the patient's value function and thus remain external to the actual decision-maker (Rangel et al., 2008).

Palliative care has the potential to improve outcomes for all of those who are affected by dementia. This approach has been shown to increase decision-makers' satisfaction with decision-making and improve quality of life by stabilizing functions and maximizing comfort of patients with advanced dementia (Kavalieratos et al., 2016; van der Steen et al., 2014). Palliative care defines treatment options for advanced dementia patients based on three goals, more than one of which may apply at the same time: 1. prolongation of life (e.g., curative treatments such as antibiotics); 2. maintenance of function (e.g., watchful waiting or treatment trial); and 3. maximization of comfort (e.g., medication to control pain and distress only) (Mitchell et al., 2017; van der Steen et al., 2014). While the maintenance of function and maximization of comfort should be prioritized in advanced dementia, it is also appropriate to prolong life if preferred (Swiss Academy of Medical Sciences, 2017; van der Steen et al., 2014). Although palliative care is a promising avenue for high-quality decisions, its implementation is still at its infancy and decision-makers may not be aware of the set of available treatment options offered by this approach.

Proxy counseling by health care providers offers an opportunity to define the goals of care of the patient, go through the process of decision-making as described above, and

promote palliative care. Proxies who have had a goals of care discussion with health care providers are more likely to prefer comfort care (Mitchell et al., 2017). This suggests that proxy counseling can help promote decisions toward more comfort-focused care. Proxy counseling may also be key in promoting awareness of the limited remaining lifetime of advanced dementia patients. In CASCADE, residents of family members who had a better understanding of what to expect in advanced dementia underwent less burdensome interventions, such as hospitalizations, intravenous therapy, and tube-feeding in the last months of life (Mitchell et al., 2009). However, this association has only been shown in a small cohort of residents who had passed away. Given the communication challenges discussed in the preceding chapter, it seems crucial to advance our understanding of factors associated with optimal counseling and decision-making.

Decision-support tools can improve decision-making by fostering communication and by informing and framing treatment choices (Stacey et al., 2014). In advanced dementia, the few decision-support tools that have been shown to improve knowledge and reduce decisional conflict of family decision-makers, and promote preferences for more comfort-focused care (Einterz, Gilliam, Lin, McBride, & Hanson, 2014; Hanson et al., 2011; 2017; Mitchell, Tetroe, & O'Connor, 2001; Snyder, Caprio, Wessell, Lin, & Hanson, 2013; Volandes, Barry, Chang, & Paasche-Orlow, 2009a; Volandes, Paasche-Orlow, Barry, Gillick, Minaker, et al., 2009b). While these tools have been found to be effective, they are tailored to families only. Moreover, most of them are video-based, expensive and difficult to implement in health care settings.

High-quality decision-making is critical in order to reflect the patient's goals of care and can be promoted via proxy counseling and decision support tools. Decision-makers can

make appropriate treatment decisions if they understand the set of available care options and their consequences. While comfort-focused care may be the preferred palliative care approach in frail patients, palliative medicine can also provide curative treatment with the goal of prolonging life, if preferred.

2. Research Plan

Advanced dementia is characterized by profound deficits and clinical complications that may result in a poor existence in the last years of life of patients (Hendriks et al., 2014; Mitchell et al., 2009). Medical decision-making by proxy surrogates and physicians is a means by which the patient can *stabilize* or *maintain functional ability* and thus obtain a better quality of life (World Health Organization, 2015b). However, processes of medical decision-making are frequently suboptimal, thereby limiting *well-being* and *healthy ageing* for both the decision-maker and the patient.

2.1. Research Questions and Empirical Studies

The research questions and empirical studies of this thesis are illustrated in Figure 1 using an extension of the Quality of Care Donabedian model (Donabedian, 1988; Teno, Landrum, & Lynn, 1997).

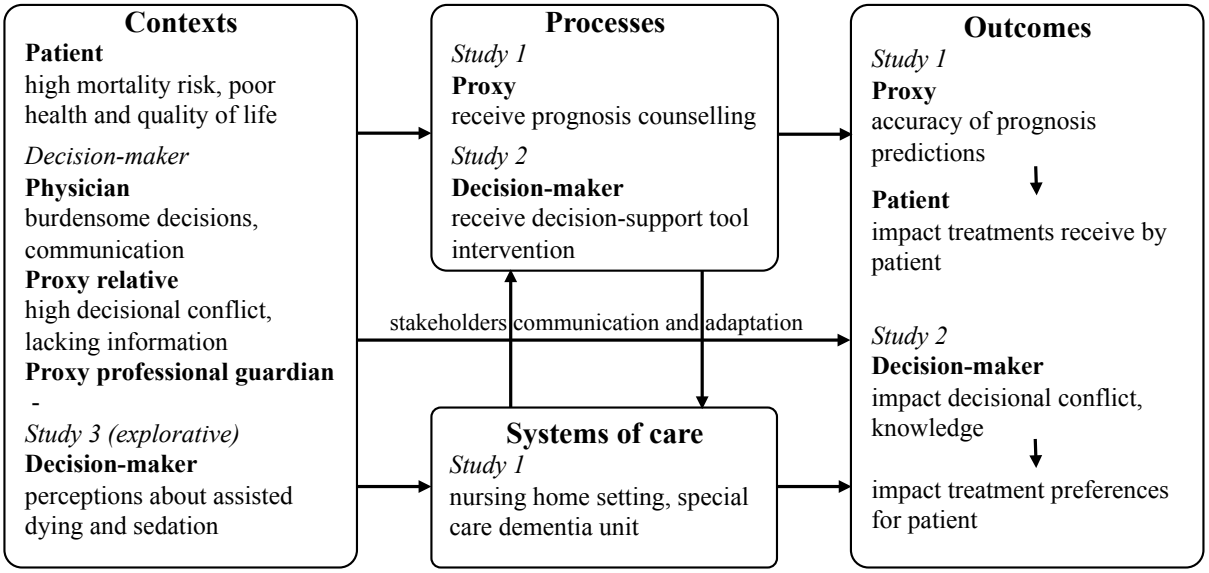

Figure 1. Illustration of research questions in studies 1-3 using the Quality of Care Model

According to this conceptual model, improved quality arises from on-going interactions between the following domains: *Contexts*, *Processes*, *Systems of care*, and *Outcomes*. The capacity of stakeholders to adapt and communicate in this environment is key to improve quality of decision-making.

In advanced dementia, the *contexts* of decision-making are broadly divided into patients and decision-makers. Advanced dementia patients have a high mortality risk, poor health and quality of life (Hendriks et al., 2014; Mitchell et al., 2009). Decision-makers report a lack of information, challenging communication, high decisional conflict, and thus burdensome decision-making in general (Engel et al., 2006; Givens et al., 2009; Pautex et al., 2013; You et al., 2015). Decision-making can be improved by *proceses*, which can be any kind of (im-)material support, such as proxy counseling or decision-support tools. The *systems of care* include the hospital, nursing home, or any special dementia care unit. *Outcomes* of decision-making on behalf of someone else are twofold (see Rangel et al., 2008 internal and external states): the decision-makers' outcomes and the observed patient's outcomes. Given the complex nature of the *contexts* of decision-making and the *systems of care*, this thesis sought to address the following question:

How can we better understand and promote medical decision-making in advanced dementia among various decision-makers? In particular, what is the relationship between decision-making supports (i.e., processes) and health outcomes of both decision-makers and patients?

To address the main question of this thesis, we have explored medical decision-making in three different, but complementary studies. All studies (1, 2, and 3) investigate *contexts* of decision-making. Studies 1 and 2 examine *processes* of decision-making such as

proxy counseling and decision-support interventions and their effects on *outcomes* in both decision-makers (studies 1 and 2) and patients (study 1 only). While study 2 is based on hypothetical situations, study 1 is conducted in nursing home settings and thus also addresses *systems of care*. Unlike studies 1 and 2, study 3 solely explores perceptions of decision-makers about controversial end-of-life practices. The main research question of this thesis is thus split into two experimental questions and one exploratory question:

How does proxy perception of prognosis relate to high-quality decision-making and care? (study 1) *How do brief decision-support tools tailored to various decision-makers relate to high-quality decision-making?* (study 2) *When reducing burden may mean choosing death: what are the perceptions of various decision-makers about controversial end-of-life practices?* (study 3, explorative)

2.1.1. Study 1: How does proxy perception of prognosis relate to high-quality decision-making and care?

Prognosis in advanced dementia is challenging and may influence care. Prior research has shown that rigorously derived mortality risk scores for advanced dementia are only moderately accurate in predicting 6-month survival (Mitchell, Kiely, Hamel, Park, Morris, et al., 2004b; Mitchell, Miller, Teno, Davis, & Shaffer, 2010a; Mitchell, Miller, Teno, Kiely, Davis, & Shaffer, 2010b; van der Steen, Mitchell, Frijters, Kruse, & Ribbe, 2007). Nonetheless, prior work suggests that the *perception* of prognosis may be a more important driver of end-of-life care (Cook et al., 2003; Mitchell et al., 2009; van der Steen, Helton, & Ribbe, 2009a; Weeks et al., 1998). The primary decision-makers in advanced dementia are proxies, but little is known about their *perception* of the remaining lifetime of the patient they are responsible for. Therefore, we asked the following specific research question in study 1:

Does proxy's perception of prognosis of the patient with advanced dementia play a role in high-quality decision-making and care?

The specific objectives of study 1 were to: 1. determine the accuracy of proxies' prognostic estimates, 2. identify factors associated with their prognostic estimates, and 3. examine the association between proxy perceived prognosis and whether residents experienced any of the following interventions: hospital transfers, parenteral therapy, tube feeding, venipunctures, and bladder catheterizations. In addressing these objectives, study 1 explored factors (see Figure 1, referring to *contexts* or *processes*) that influence proxies' understanding that a patient may have less than 6 months to live and evaluated whether this understanding is associated with the receipt of less burdensome interventions (see Figure 1, *outcomes* of decision-makers and patients).

2.1.2. Study 2: How do brief decision support tools tailored to various decision-makers relate to high-quality decision-making?

Antibiotics and artificial hydration may be of limited clinical benefit in advanced dementia (Givens et al., 2010; Mitchell et al., 2014; H. R. W. Pasman et al., 2005; 2006; van der Steen et al., 2012; 2014; 2017a). Relatives lack support, physicians report difficulties finding adequate language to address end-of-life decisions, and there is no data on the experience of professional guardians making end-of-life decisions (Engel et al., 2006; Givens et al., 2009; Pautex et al., 2013; You et al., 2015). The few existing decision support tools in advanced dementia are primarily videos that are tailored to only relative decision-makers and difficult to implement in nursing homes (Einterz et al., 2014; Hanson et al., 2011; 2017; Mitchell et al., 2001; Snyder et al., 2013; Volandes, Barry, Chang, & Paasche-Orlow, 2009a; Volandes, Paasche-Orlow, Barry, Gillick, Minaker, et al., 2009b). Study 2 addressed this gap

by developing brief decision support tools (two-page, pocket-sized brochures) tailored to various decision-makers on antibiotics for pneumonia and artificial hydration in advanced dementia. Study 2 was guided by the following specific research question: *Can brief decision support tools promote high-quality decision-making in various decision-makers?*

The specific objectives of study 2 were to test whether the decision support tools impact 1. decisional conflict, 2. knowledge, and 3. preferences about the use of antibiotics and artificial hydration in advanced dementia. In addressing these objectives, study 2 evaluated whether a brief and targeted decision-support tool (see Figure 1, *processes*) would result in reduced decisional conflict, increased knowledge among various decision-makers and in a shift in preferences to forego the use of burdensome treatments (see Figure 1, *outcomes* of decision-makers).

2.1.3. Study 3: When reducing burden may mean choosing death: what are perceptions of various decision-makers about controversial end-of-life practices?

Patients with advanced dementia have profound deficits and experience burdensome complications that may cause discomfort and result in a poor quality of life (Hendriks et al., 2014; Mitchell et al., 2009; van der Steen, Deliens, Koopmans, & Onwuteaka-Philipsen, 2016). Assisted dying and continuous deep sedation until death are controversial end-of-life practices that may be used as a last resort to avoid a poor quality of life and death with advance dementia (E. J. Emanuel et al., 2016; Miccinesi et al., 2006; Ziegler et al., 2018). Little is known about the perceptions of key decision-makers about these practices for patients with advanced dementia. In order to advance our understanding in this regard, we asked the following specific research question: *Do key decision-makers perceive assisted*

dying and continuous deep sedation until death as a valid end-of-life option in advanced dementia?

The specific objectives of study 3 were to: 1. describe physician and proxy perceptions about the use of assisted dying and continuous deep sedation in advanced dementia, and 2. compare their perceptions. In addressing these objectives, study 3 explored whether physicians and proxies agree with the use of controversial end-of-life practices among patients with advanced dementia (see Figure 1, *contexts*), and whether proxies are more inclined to agree with these practices than physicians.

3. Study 1: Proxy Perception of Prognosis and Treatment Decisions

Perception of Prognosis Among Proxies of Nursing Home Residents with Advanced Dementia[1]

3.1. Introduction

More than 5 million Americans have been diagnosed with Alzheimer's disease; a number projected to increase to 13.8 million by 2050 (Hebert, Weuve, Scherr, & Evans, 2013). Alzheimer's disease is the sixth most common cause of death in the United States (Kochanek, Murphy, Xu, & Tejada-Vera, 2016). Patients with advanced dementia commonly experience burdensome interventions that may be of limited benefit and do not promote comfort (Gozalo et al., 2011; Meier et al., 2001; Mitchell et al., 2003; 2009; 2014; Mitchell, Morris, Park, & Fries, 2004c; Morrison & Siu, 2000b).

Prognostication influences end-of-life care. The U.S. Medicare Hospice benefit requires an estimated life expectancy of 6 months,(The National Hospice Organization, 1996) although the prognostic accuracy of hospice guidelines for dementia patients may be little better than chance (Mitchell, Miller, Teno, Kiely, Davis, & Shaffer, 2010b). Rigorously derived mortality risk scores for this population are only moderately accurate in predicting 6-month survival (Mitchell, Kiely, Hamel, Park, Morris, et al., 2004b; Mitchell, Miller, Teno, Davis, & Shaffer, 2010a; Mitchell, Miller, Teno, Kiely, Davis, & Shaffer, 2010b; van der Steen et al., 2007). Nonetheless, prior work suggests that the *perception* of prognosis is an important driver of end-of-life care (Cook et al., 2003; Mitchell et al., 2009; van der Steen,

[1] A similar version of this chapter has been accepted for publication in the *Journal of the American Medical Association Internal Medicine* (JAMA IM) (Loizeau, Shaffer, Habtemariam, Hanson, Volandes, & Mitchell).

Helton, & Ribbe, 2009a; Weeks et al., 1998). Our group found that nursing home (NH) residents with advanced dementia whose proxies perceived they had less than 6 months to live, were less likely to get tube fed, hospitalized, or receive parenteral therapy in their last 180 days of life (Mitchell et al., 2009). However, this retrospective analysis was limited to a small decedent cohort, and did not examine factors influencing prognostic perceptions. Proxies of patients with advanced cancer and critical illness report basing their prognostic perceptions on factors such as the need to remain hopeful, religious beliefs, and patient attributes (i.e., fortitude) (Boyd et al., 2010; Chiarchiaro, Buddadhumaruk, Arnold, & White, 2015; D. B. White et al., 2016a).

To better understand proxies' perceptions of prognosis and their role in the care of NH residents with advanced dementia, we combined data from 2 studies conducted by our group: the Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia (SPREAD);(Mitchell et al., 2013; 2014) and the Educational Video to Improve Nursing home Care in End-stage dementia (EVINCE) trial (Mitchell et al., 2017). In both studies, proxies of NH residents with advanced dementia were prospectively asked every 3 months (up to 12 months) how long they felt the resident had to live. The objectives were to: (1) determine the accuracy of proxies' prognostic estimates, (2) identify factors associated with their prognostic estimates, and (3) examine the association between proxies' perceived prognosis and the residents' receipt of potentially burdensome interventions.

3.2. Methods

Data Sources

Data were leveraged from 2 studies with identically defined populations and data collection methods for the variables used in this study: (1) SPREAD: Study of Pathogen

Resistance and Exposure to Antimicrobials in Dementia;(Mitchell et al., 2013; 2014) and (2) EVINCE: Educational Video to Improve Nursing home Care in End-stage dementia (Mitchell et al., 2017). The SPREAD study was a prospective cohort study conducted from September 2009 through November 2012 in which 362 NH residents with advanced dementia were followed in 35 Boston area facilities for 12 months to describe infection management. The EVINCE study was a cluster randomized clinical trial conducted in 62 Boston area facilities (intervention, N=31; control, N=31) conducted from March 2013 to July 2017. Proxies of NH residents with advanced dementia in intervention facilities (N=212) were exposed to an advance care planning video whereas those in the control facilities (N=190) experienced usual care. Residents were followed for 12 months. Observational data from the intervention and control arms were combined for this study.

Hebrew SeniorLife Institutional Review Board approved the conduct of both studies. Proxies provided informed consent for the residents' and their own participation. They were not compensated.

Study Population

Recruitment procedures were the same in both studies. Resident eligibility criteria included: (1) age 65 years or older, (2) dementia (any type), (3) Global Deterioration Scale (GDS) score of 7 (from nurse; range, 1-7; higher scores indicate worse dementia),(Reisberg et al., 1982) (4) available English-speaking proxy, and (5) NH stay longer than 90 days. A GDS score of 7 is characterized by profound memory deficits (cannot recognize family), verbal ability of less than 5 words, incontinence, and non ambulatory status. Every 3 months, research assistants (RAs) asked nurses on each NH unit to identify eligible residents.

Dementia diagnosis, age, and proxy availability were confirmed by medical chart review. Proxies were the residents' formally or informally designated medical decision-makers.

Data Elements

All variables were collected and defined similarly in both studies, unless otherwise stated. Residents' charts were abstracted and proxies were interviewed by RAs at baseline and quarterly thereafter for up to 12 months. If the resident died, the medical chart was reviewed within 14 days of death. Proxy interviews were conducted by telephone except for in-person baseline interviews in EVINCE.

This study focused on the following question asked at all proxy interviews: "In your opinion, how close do you feel [resident] is to the end of her/his life?", with the following response options: (1) less than 1 month, (2) 1 to 6 months, (3) 7 to 12 months, (4) longer than 12 months, and (5) do not know or refused.

Two other outcomes were examined; death and use of burdensome interventions. The RAs contacted nursing units bimonthly to determine if any residents had died, and if so the date of death. At each assessment, the following potentially burdensome interventions experienced by residents since the prior assessment were abstracted from their charts: hospital transfers (hospitalizations or emergency room visits), parenteral therapy for hydration or medication administration, new feeding tube insertion, venipunctures, and bladder catheterizations to work-up suspected urinary tract infections (only available in SPREAD). We selected these interventions as they were potential sources of discomfort in frail older persons,(Morrison et al., 1998) and generally do not reflect comfort-focused care.

Other variables were used to describe residents and proxies, and included as covariates (Boyd et al., 2010; Chiarchiaro et al., 2015; Cook et al., 2003; Mitchell et al.,

2009; van der Steen, Helton, & Ribbe, 2009a; Weeks et al., 1998; D. B. White et al., 2016a). Baseline resident data included: demographics (age, sex, and race (white vs other)), etiology of dementia (Alzheimer's disease vs other), common comorbidities (chronic obstructive pulmonary disease, congestive heart failure, and diabetes), Test for Severe Impairment (TSI) score obtained by direct resident examination (range, 0-24; lower scores indicate greater cognitive impairment; dichotomized to equal to vs greater than 0),(Albert & Cohen, 1992) and functional status by nurse interview using the Bedford Alzheimer's Nursing Severity-Subscale (BANS-S; range, 7-28; higher scores indicate greater functional disability) (Volicer, Hurley, Lathi, & Kowall, 1994). At every assessment, it was determined whether the resident experienced any of the following new major illnesses since the prior assessment: hip fracture, stroke, myocardial infarction, major gastrointestinal bleed, pneumonia, and new diagnosis of cancer (other than localized skin cancer).

Baseline proxy data included: age, sex, years as proxy, and relationship to resident (child vs other). At all interviews, proxies were asked whether any NH clinicians had asked their opinion about the resident's goal of care (yes/no).

Analysis

Analyses were conducted using SAS statistical software (version 9.4, SAS Institute). Main results were generated for the combined cohorts and presented for each study separately in Appendices A1, A2, and A3. Means (SDs), and frequencies were used to describe continuous and categorical variables, respectively.

Cumulative incidence of death was displayed graphically and compared between SPREAD and EVINCE using survival analysis. For residents who died, survival time was calculated as the number of days between the date of baseline proxy interview and date of

resident death. For all analyses examining survival as an outcome, residents who survived the follow-up period were censored at 12 months and those lost to follow-up were censored at the last known follow-up date.

Cox proportional hazards regression examined the accuracy of proxies' prognostic estimates (independent variable) as ascertained from all interviews and analyzed as time-varying variables. A prognostic estimate later than 12 months was the referent category. The model examined the association between the prognostic estimates at a particular interview date and the risk of the resident dying given that the resident had survived up until that point. Because response options did not include prognostic estimates between 6 and 7 months, actual survival times during that interval were rounded up or down. Robust standard errors accounted for clustering at the facility-level. Adjusted hazard ratios (AHRs) and 95% confidence intervals (CIs) were computed. A generalized version of the *c* statistic allowing for censored data was calculated as a measure of the model's overall accuracy (range 0.5-1, higher scores indicate greater accuracy) (Mayo Foundation for Medical Education and Research). A sensitivity analysis excluded proxies in the EVINCE intervention group because the video could have influenced the accuracy of their prognostic estimates.

Logistic regression was used to identify resident and proxy characteristics (independent variables) associated with a proxy prognostic estimate of less than 6 months (outcome). The prognosis variable was dichotomized because the proportion of interviews at which proxies estimated prognosis to be less than 1 month and 1 to 6 months were too small to examine as separate categories. Interviews at which the proxy responded "do not know" or refused to answer were excluded. The analysis was conducted at the level of assessment intervals. Independent variables considered a priori to be possibly associated with

prognostication, (Boyd et al., 2010; Chiarchiaro et al., 2015; Mitchell et al., 2009; D. B. White et al., 2016a) included; resident demographics (age [dichotomized at median], sex, race), dementia type, comorbidities, TSI, BANS-S, hospital transfer in prior 3 months, proxy demographics (age (dichotomized at median), gender), proxy relationship to resident, and goals of care discussions. Proxy prognostic estimates and other dynamic independent variables (e.g., hospital transfers) were ascertained from each assessment. Static variables (e.g., sex) were brought forward from baseline. Bivariable analyses examined the unadjusted associations between each independent variable and prognosis at a given assessment interval. Variables associated with the outcome at $P < .10$ in the unadjusted analyses were entered into a multivariable model. Generalized estimating equations (GEE) accounted for clustering among residents/proxy dyads. Odds ratios (ORs) with 95% CIs were computed.

Finally, logistic regression was used to examine the association between a proxy prognostic estimate of less than 6 months (main independent variable) and the use of any of the following burdensome interventions (outcome): hospital transfer, parenteral therapy, new feeding tube, venipuncture, and bladder catheterization. The analysis was conducted at the level of assessment intervals and excluded assessments with "do not know/refused" responses to the prognosis question. Prognosis was derived from the interview conducted at the beginning of a given 3-month interval. The outcome was defined as whether the resident experienced a burdensome intervention during the 3-month interval following that interview. Covariates considered a priori to be possibly associated with intervention use (Cook et al., 2003; Mitchell et al., 2009; van der Steen, Helton, & Ribbe, 2009a; Weeks et al., 1998) included: resident demographics, dementia type, comorbidities, TSI, BANS-S, new major illness, proxy demographics, proxy relationship to resident, and goals of care discussions. Dynamic covariates were drawn from the assessment that best related the resident's status

during the interval. For example, occurrence of a major illness was ascertained from the medical chart review done at the end of the interval, which recorded events during the interval. Being asked about goals of care was drawn from the interview at the start of the interval. Static variables were brought forward from baseline. Bivariable followed by multivariable analyses were conducted as described above and GEE accounted for clustering among resident/proxy dyads. Odds ratios with 95% CIs were computed.

3.3. Results

Resident and Proxy Characteristics

Baseline characteristics were comparable between the 2 studies (SPREAD, N=362 dyads; EVINCE, N=402 dyads) (Table 1). Resident characteristics of the combined cohort (N=764 dyads) included: mean (SD) age, 86.6 (7.3) years; female, 631 (82.6%); and white, 685 (89.7%). A total of 412 (53.9%) residents had TSI scores equal to 0, and their mean (SD) BANS-S score was 20.6 (2.8), indicating severe cognitive and functional impairment, respectively. Proxy characteristics were: mean (SD) age, 61.4 (10.6) years; female, 492 (64.4%); years as proxy, 8.8 (6.3); and child of resident, 489 (64.0%).

Table 1. Baseline characteristics of nursing home residents with advanced dementia and their proxies

Characteristics	SPREAD and EVINCE combined (N=764)[a]	SPREAD (N=362)	EVINCE (N=402)
Resident			
Age (years), mean ± standard deviation	86.6 ± 7.3	86.5 ± 7.3	86.7 ± 7.4
Age > 87 (median)	362 (47.4)	174 (48.1)	188 (46.8)
Female, %	631 (82.6)	308 (85.1)	323 (80.3)
White (vs other), %	685 (89.7)	335 (92.5)	350 (87.1)
Alzheimer's disease (vs other), %	552 (72.3)	269 (74.3)	283 (70.4)
Chronic obstructive pulmonary disease, %	90 (11.8)	42 (11.6)	48 (11.9)
Congestive heart failure, %	120 (15.7)	63 (17.4)	57 (14.2)
Diabetes, %	146 (19.1)	67 (18.5)	79 (19.7)
TSI = 0 (vs greater than 0), %[b]	412 (53.9)	222 (61.3)	190 (47.3)
BANS-S, mean ± standard deviation[c]	20.6 ± 2.8	21.2 ± 2.7	20.1 ± 2.8
BANS-S > 21 (median)	328 (42.9)	182 (50.3)	146 (36.3)
Enrolled in hospice	105 (13.7)	31 (8.6)	74 (18.4)
Died during 12 month follow-up, %	310 (40.6)	135 (37.3)	175 (43.5)
Proxy			
Age (years), mean ± standard deviation[d]	61.4 ± 10.6	60.4 ± 10.3	62.3 ± 10.8
Age > 61 (median)	348 (45.6)	153 (42.3)	195 (48.5)
Female, %	492 (64.4)	226 (62.4)	266 (66.2)
Years as proxy, mean ± standard deviation[d]	8.8 ± 6.3	8.1 ± 5.7	9.4 ± 6.8
Child of resident (vs other), %	489 (64.0)	233 (64.4)	256 (63.7)
Prognostic estimates of resident survival at the baseline interviews only, %			
<1 month	10 (1.3)	3 (0.8)	7 (1.7)
1-6 months	75 (9.8)	29 (8.0)	46 (11.4)
7-12 months	148 (19.4)	59 (16.3)	89 (22.1)
>12 months	477 (62.4)	240 (66.3)	237 (59.0)
Don't know or refused to answer	54 (7.1)	31 (8.6)	23 (5.7)

[a]*SPREAD = the Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia; EVINCE = the Educational Video to Improve Nursing home Care in End-stage dementia.*

[b]*TSI = Test for Severe Impairment, range 0-24, lower scores indicate greater cognitive impairment.*

[c]*BANS-S = Bedford Alzheimer's Nursing Severity-Subscale, range 7-28, higher scores indicate more functional disability.*

[d]*Data missing for proxy age (N=10) and years as proxy (N=5).*

Survival and Accuracy of Proxy Prognostic Estimates

In the combined cohort, 310 (40.6%) residents died, and 11 (1.4%) were lost to follow-up. In SPREAD, 135 (37.3%) residents died and 5 (1.4%) were lost to follow-up. In EVINCE, 175 (43.5%) residents died and 6 (1.5%) were lost to follow-up. Six-month mortality rates were: combined cohort, 195 (25.5%); SPREAD, 88 (24.3%); and EVINCE, 107 (26.6%). The Figure 2 shows the cumulative incidences of death for the combined cohort, and each cohort separately which did not differ significantly (log rank P = .08).

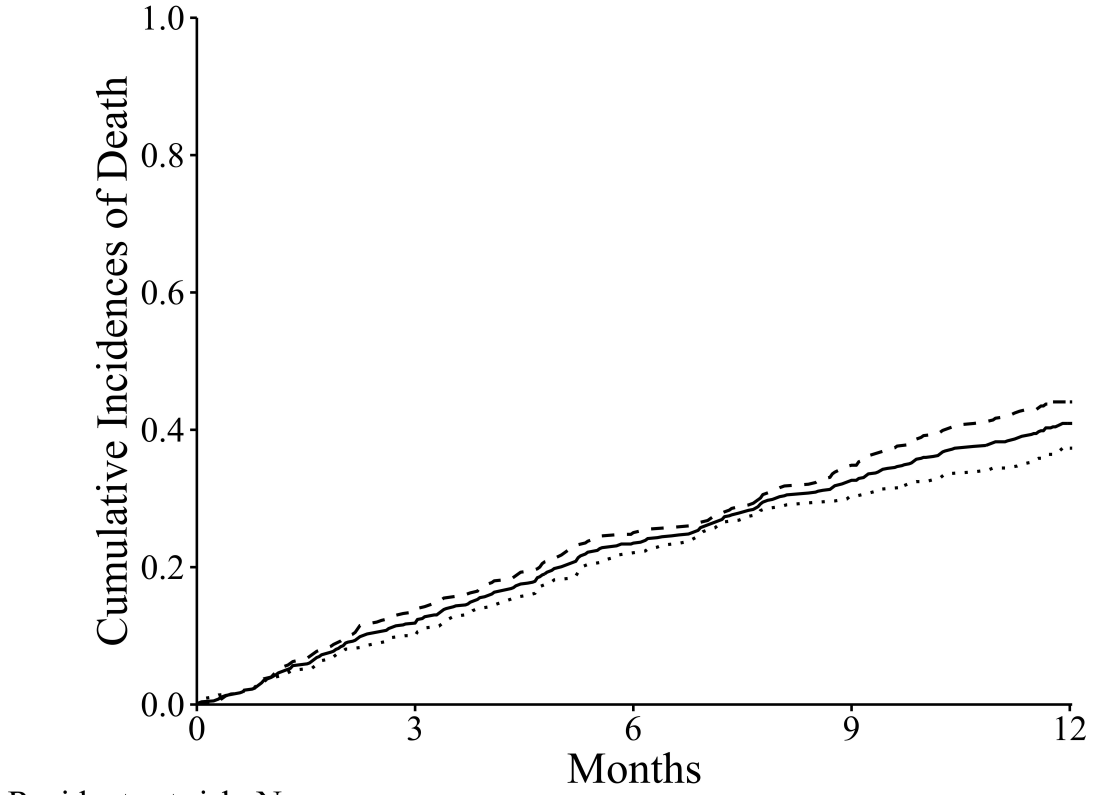

Figure 2. Cumulative incidences of death among 764 nursing home residents with advanced dementia.

Cumulative incidences of death among nursing home residents with advanced dementia in the Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia study (N=362; dotted line) and the Educational Video to Improve Nursing Home Care in End-stage dementia study (N=402; dashed line), and two studies combined (N=764; solid line).

At baseline, proxies' estimates of the resident prognosis were: less than 1 month, 10 (1.3%); 1 to 6 months, 75 (9.8%); 7 to 12 months, 148 (19.4%); longer than 12 months, 477 (62.4%); and do not know/refused, N=54 (7.1%). At all proxy interviews (i.e., baseline and follow-up) (2649), proxy prognostic estimates were: less than 1 month, 30 (1.1%); 1 to 6 months, 279 (10.5%); 7 to 12 months, 664 (25.1%); longer than 12 months, 1553 (58.6%); and do not know/refused, 123 (4.6%). In the Cox model, the likelihood of dying was higher among residents whose proxies thought they had a shorter prognosis (referent, longer than 12 months): less than 1 month (AHR, 27.53; 95% CI, 15.81, 47.95); 1 to 6 months (AHR, 4.61; 95% CI, 3.12, 6.79); 7 to 12 months (AHR, 1.91; 95% CI, 1.38, 2.64); and do not know/refused (AHR, 0.92; 95% CI, 0.40, 2.14). The model's *c* statistic was 0.67. Results were similar when analyzed in the EVINCE cohort with the intervention arm excluded: less than 1 month, AHR, 28.77; 95% CI, 13.99, 59.18; 1 to 6 months, AHR, 4.89; 95% CI, 3.10, 7.71; 7 to 12 months, AHR, 2.05; 95% CI, 1.43, 2.94; and don't know/refused, AHR, 1.04; 95% CI, 0.39, 2.78. The *c* statistic was 0.67.

Factors Associated with Proxy Prognostication

The proportion of all interviews (2526) at which proxies stated the resident had less than 6 months was 12.2% (309). In unadjusted analyses, variables associated with a proxy prognostic estimate of less than 6 months at a $P < .10$ were: resident age older than 87 years, female proxy, and being asked about goals of care (Table 2). In the multivariable model, only having been asked about goals of care (adjusted odds ratio [AOR], 1.94; 95% CI, 1.50, 2.52) and female proxy (AOR, 1.55; 95% CI, 1.09, 2.20) remained significantly associated with a prognostic estimate of less than 6 months.

Table 2. Association between characteristics of nursing home residents with advanced dementia and their proxies and the proxy's perception that the resident had less than 6 months to live[a]

Characteristic	Total No. (%) of Assessment Intervals with Characteristic[a] (N=2526)	No. (%) of Assessment Intervals in Which Proxy Estimated Resident had < 6 Months to Live (N=309)		Odds Ratio[b] for Proxy Perceived Prognosis (95% Confidence Interval)	
		With Characteristic Present	With Characteristic Absent	Unadjusted	Adjusted
Resident					
Age > 87 (median)	1178 (46.6)	164 (6.5)	145 (5.7)	1.34 (0.96, 1.88)[c]	
Female	2110 (83.5)	248 (9.8)	61 (2.4)	0.78 (0.50, 1.21)	
White	2272 (89.9)	279 (11.1)	30 (1.2)	1.05 (0.56, 1.96)	
Alzheimer's disease	1813 (71.8)	216 (8.6)	93 (3.7)	0.90 (0.62, 1.31)	
Chronic obstructive pulmonary disease	264 (10.5)	43 (1.7)	266 (10.5)	1.46 (0.92, 2.32)	
Congestive heart failure	387 (15.3)	52 (2.1)	257 (10.2)	1.14 (0.71, 1.81)	
Diabetes	454 (18.0)	56 (2.2)	253 (10.0)	1.01 (0.66, 1.56)	
TSI = 0[d]	1315 (52.1)	165 (6.5)	144 (5.7)	1.06 (0.76, 1.49)	
BANS-S > 21 (median)[e]	996 (39.4)	129 (5.1)	180 (7.1)	1.12 (0.80, 1.56)	
Any hospital transfer in prior 3 months[f]	100 (4.0)	17 (0.7)	292 (11.6)	1.50 (0.86, 2.60)	
Proxy					
Age > 61 (median)[g]	1186 (47.4)	158 (6.3)	149 (6.0)	1.20 (0.86, 1.69)	
Female	1613 (63.9)	224 (8.9)	85 (3.4)	1.57 (1.10, 2.24)[c]	1.55 (1.09, 2.20)
Child of resident	1565 (62.0)	200 (7.9)	109 (4.3)	1.15 (0.80, 1.65)	
Asked their opinion about goals of care by a nursing home clinician	1126 (44.6)	183 (7.2)	126 (5.0)	1.96 (1.52, 2.54)[c]	1.94 (1.50, 2.52)

[a]*Analyses were done at the level of assessment intervals, which included all baseline and follow-up resident/proxy assessment intervals (N=2526). Resident chart reviews and proxy interviews were done at baseline and quarterly for up to 12 months. Static variables were brought forward from baseline. Proxy's perception of prognosis and other dynamic variables (e.g., goals of care discussion, hospital transfers) were ascertained from each assessment period. Proxies stated the resident had less than 6 months to live at 12.2% of all baseline and follow-up assessment intervals (309 of 2526).*

[b]*Unadjusted and adjusted odds ratio accounted for clustering among resident/proxy dyads using generalized estimating equations.*

[c]*Variables that were significant at P < 0.10 in bivariable analyses and entered into the multivariable model.*

[d]*TSI = Test for Severe Impairment, range 0-24, lower scores indicate greater cognitive impairment.*

[e]*BANS-S = Bedford Alzheimer's Nursing Severity-Subscale, range 7-28, higher scores indicate greater functional disability.*

[f]*Hospital transfer included hospitalization or emergency room visit.*

[g]*Age missing for 24 proxies.*

Table 3. Association between proxy perception of prognosis and use of burdensome interventions[a] among nursing home residents with advanced dementia

Characteristic	Total No. (%) of Assessment Intervals with Characteristic[b] (N=2031)	No. (%) of Assessment Intervals in Which Resident had Any Burdensome Interventions (N=1097)		Likelihood of a Burdensome Intervention OR[c] (95% Confidence Interval)	
		With Characteristic Present	With Characteristic Absent	Unadjusted	Adjusted
Proxy Estimated Resident had < 6 Months to Live	251 (12.4)	89 (4.4)	1008 (49.6)	0.47 (0.35, 0.62)[d]	0.46 (0.34, 0.62)
Resident Covariates					
Age > 87 (median)	954 (47.0)	490 (24.1)	607 (29.9)	0.81 (0.64, 1.02)[d]	0.77 (0.61, 0.97)
Female	1691 (83.3)	917 (45.2)	180 (8.9)	1.13 (0.83, 1.52)	
White	1837 (90.5)	970 (47.8)	127 (6.3)	0.58 (0.40, 0.86)[d]	
Alzheimer's disease	1472 (72.5)	781 (38.5)	316 (15.6)	0.89 (0.69, 1.14)	
Chronic obstructive pulmonary disease	217 (10.7)	120 (5.9)	977 (48.1)	1.00 (0.69, 1.44)	
Congestive heart failure	318 (15.7)	203 (10.0)	894 (44.0)	1.63 (1.19, 2.22)[d]	1.63 (1.19, 2.24)
Diabetes	357 (17.6)	243 (12.0)	854 (42.1)	1.94 (1.41, 2.67)[d]	1.91 (1.39, 2.63)
TSI = 0[e]	1053 (51.9)	501 (24.7)	596 (29.4)	0.57 (0.46, 0.72)[d]	0.66 (0.52, 0.86)
BANS-S > 21 (median)[f]	808 (39.8)	373 (18.4)	724 (35.7)	0.58 (0.46, 0.74)[d]	0.68 (0.53, 0.88)
Any new major illness in prior 3 months[g]	109 (5.4)	82 (4.0)	1015 (50.0)	2.59 (1.70, 3.96)[d]	2.83 (1.84, 4.35)
Proxy Covariates					
Age > 61 (median)[h]	941 (46.3)	481 (23.7)	606 (29.8)	0.78 (0.62, 0.98)[d]	
Female	1288 (63.4)	671 (33.0)	426 (21.0)	0.86 (0.68, 1.08)	
Child of resident	1268 (62.4)	709 (34.9)	388 (19.1)	1.22 (0.97, 1.55)[d]	
Asked their opinion about goals of care by a nursing home clinician	953 (46.9)	501 (24.7)	596 (29.4)	0.88 (0.74, 1.04)	

[a] *Burdensome interventions included any of the following: hospital transfer (hospitalization or emergency room visits), parenteral therapy, new feeding tube insertion, venipuncture, and bladder catheterizations.*

[b] *Analyses were done at the level of assessment intervals, which included baseline and follow-up resident/proxy assessment intervals (N=2031). Proxy prognosis was taken from the interview done at the start of the interval. The use of burdensome interventions reflected the residents experience during the 3-month interval following that interview. Dynamic covariates were drawn from the assessment that best reflected the resident's status during the interval of interest (e.g., any new major illness). Static variables were brought forward from baseline.*

[c] *Unadjusted and adjusted odds ratio accounted for clustering among resident/proxy dyads using generalized estimating equations.*

[d] *Variables that were significant at P < 0.10 in bivariable analyses and entered into the multivariable model.*

[e] *TSI = Test for Severe Impairment, range 0-24, lower scores indicate greater cognitive impairment.*

[f] *BANS-S = Bedford Alzheimer's Nursing Severity-Subscale, range 7-28, higher scores indicate more disability.*

[g] *Any new major illness included hip fracture, stroke, myocardial infarction, major gastrointestinal bleed, pneumonia, and/or new diagnosis of cancer (other than localized skin cancer).*

[h] *Age missing for 18 proxies.*

Use of Burdensome Interventions

There were 2031 resident-assessment intervals available to examine the use of burdensome interventions over the follow-up period. The proportion of intervals during which residents experienced burdensome interventions were: hospital transfer, 68 (3.3%); parenteral therapy, 49 (2.4%); new feeding tube, 3 (0.1%); venipuncture, 1048 (51.6%); bladder catheterizations, 157 (7.7%); and any intervention, 1097 (54.0%). In unadjusted analyses, factors associated with a lower likelihood of any burdensome intervention use at $P < 0.10$ included: proxy prognosis of less than 6 months, resident age older than 87 years, white resident, TSI equal to 0, BANS-S greater than 21, proxy age older than 61 years, and child of resident (Table 3). Congestive heart failure, diabetes, and any new major illness were associated with a greater likelihood of receiving a burdensome intervention. After multivariable adjustment, a prognostic estimate of less than 6 months remained significantly associated with a lower likelihood of the resident receiving any burdensome interventions (AOR, 0.46; 95% CI, 0.34, 0.62).

3.4. Discussion

In this study, proxies of NH residents with advanced dementia predicted how long the resident would live with moderate accuracy. Having been asked about their opinion about the goals of care was the factor most strongly associated with the proxies' perception that the resident had less than 6 months to live. Residents were significantly less likely to experience burdensome interventions when their proxies perceived they would die within 6 months.

The accuracy of the proxy's prognostic estimates was modest, but remarkably identical to the empirically derived Advanced Dementia Prognostic Tool (*c* statistic, 0.67), and better than hospice guidelines for dementia (*c* statistic, 0.55) (Mitchell, Miller, Teno,

Kiely, Davis, & Shaffer, 2010b). Prognostic estimates of proxies of patients in intensive care units are reportedly somewhat more accurate (*c* statistic, 0.74),(D. B. White et al., 2016a) perhaps because it is easier to recognize impending death in the context of critical illness. We found a minority of proxies believed the resident would die within 6 months, and that they underestimated mortality; 40.6% of residents died after 12 months but at baseline only 30.5% of proxies perceived the resident would die in 12 months. An overly optimistic perception of prognosis is a consistent finding among proxies, patients, and clinicians in the context of other serious illnesses (Fried, Bradley, & O'Leary, 2006; Weeks et al., 1998; D. B. White et al., 2016a; N. White, Reid, Harris, Harries, & Stone, 2016b).

Having been asked their opinion about the goals of care by NH clinicians was most strongly associated with proxies' perception that the resident had less than 6 months to live. Given that the question referred to a time period before the proxy interview, renders it less likely the association was owing to proxies seeking out goals of care discussions as a consequence of believing the resident may die soon. Although we did not ascertain the contents of these conversations, research from the critical care setting found that clinicians make prognostic statements of some nature in most discussions about goals of care (D. B. White, Engelberg, Wenrich, Lo, & Curtis, 2007).

This study supports and furthers research suggesting that patients whose proxies believe they are close to the end-of-life are more likely to opt for comfort-focused care,(Mitchell et al., 2017) and receive fewer burdensome interventions (Cook et al., 2003; Mitchell et al., 2009; van der Steen, Helton, & Ribbe, 2009a; Weeks et al., 1998). A cross-sectional analysis of baseline EVINCE data found that proxies who perceived that the resident had a life expectancy of less than 6 months were significantly more likely to prefer a

level of care that only included treatments to reduce suffering vs one that included potentially life-prolonging but uncomfortable interventions (AOR, 12.25; 95% CI, 4.04, 37.08) (Mitchell et al., 2017). The interventions considered potentially burdensome in this study are not indicative of comfort-focused care. Even venipunctures and bladder catheterizations, which may be considered relatively benign, can be a source of discomfort in these very frail residents and generally are not undertaken when the goal of care is solely comfort (Morrison et al., 1998).

Several limitations of this report deserve comment. First, the study was limited to a primarily white cohort in Boston area NHs, and thus findings may not be generalizable to other regions or populations. Second, proxies selected their prognostic estimates from categories of expected survival. Alternative approaches, such as estimating the probability of surviving a given time frame (probability approach), asking about life expectancy in a more open-ended fashion (temporal approach) or the "surprise question" method, may yield different prognostic accuracies (Perez-Cruz et al., 2014; N. White et al., 2016b; N. White, Kupeli, Vickerstaff, & Stone, 2017). Third, we could not assess the accuracy of the proxies' reports about being asked about goals of care or which aspects of these discussions may have influenced their prognostic estimates. It is likely that factors not captured in the dataset impacted those perceptions,(Boyd et al., 2010; Chiarchiaro et al., 2015; D. B. White et al., 2016a) but require a qualitative approach to elucidate.

This report demonstrates that proxies are moderately accurate in estimating how long NH residents with advanced dementia will live. Regardless of accuracy, the proxy's perception that the resident may die within 6 months was associated with the use of fewer burdensome interventions. Goals of care discussions with clinicians may be important for

proxies to gain that perception. In advanced dementia, in which highly accurate prognostication can be elusive, an understanding of the terminal nature of this condition may be pertinent to promoting a comfort-focused approach to care.

4. Study 2: Decision Support Tools for Treatment Decisions

Fact Box Decision Support Tools for Antibiotics for Pneumonia and Artificial Hydration in Advanced Dementia: a Randomized Controlled Trial [2]

4.1. Introduction

Advanced dementia is associated with a high mortality risk and characterized by repeated pneumonia episodes and reduced oral intake (Mitchell et al., 2009; van der Steen et al., 2006). Consequently, patients commonly receive antibiotics and artificial hydration, but these interventions can be burdensome and have questionable benefit at the end-of-life (Givens et al., 2010; Mitchell et al., 2014; H. R. W. Pasman et al., 2005; 2006; van der Steen et al., 2012; 2014; 2017a).

The majority of surrogate decision-makers for advanced dementia patients are family members. These family members report lack of adequate decision support from health care providers,(Engel et al., 2006; Givens et al., 2009) which may lead to uninformed treatment decisions that do not align with goals of care (Mitchell et al., 2009; 2014; 2017). Prior research shows that when families receive provider counseling, advanced dementia patients are less likely to undergo burdensome interventions in their last months of life (Mitchell et al., 2009). In the absence of relatives, treatment decisions are made by professional guardians, but data on their experience making choices about end-of-life care is lacking.

[2] A similar version of this chapter is under revision at *Age & Ageing* (Loizeau, Theill, Cohen, Eicher, Mitchell, Meier, McDowell, Martin, & Riese).

Decision support tools improve medical decision-making by improving knowledge and reducing decisional conflict (Einterz et al., 2014; Hanson et al., 2011; Mitchell et al., 2001; Snyder et al., 2013; Volandes, Barry, Chang, & Paasche-Orlow, 2009a). The few decision support tools designed specifically for proxies of patients with advanced dementia promote preferences for more comfort-focused care (Einterz et al., 2014; Hanson et al., 2011; 2017; Volandes, Barry, Chang, & Paasche-Orlow, 2009a; Volandes, Paasche-Orlow, Barry, Gillick, Minaker, et al., 2009b). A prior randomized controlled trial (RCT) showed that a 20-minute, paper-print decision support tool about feeding options in advanced dementia reduced surrogates' decisional conflict, improved their knowledge, fostered communication with providers, and resulted in residents receiving increased eating assistance (Hanson et al., 2011). While these tools have been found to be effective, they are tailored to only a single group of decision makers (Einterz et al., 2014; Hanson et al., 2011; 2017; Mitchell et al., 2001; Snyder et al., 2013; Volandes, Barry, Chang, & Paasche-Orlow, 2009a; Volandes, Paasche-Orlow, Barry, Gillick, Minaker, et al., 2009b).

Fact Boxes are short, inexpensive, paper-based decision support tools that are tailored for a variety of decision-makers. Using simple, understandable language, they present balanced information on the benefits and harms of receiving versus not receiving a treatment (McDowell, Rebitschek, Gigerenzer, & Wegwarth, 2016; Schwartz, Woloshin, & Welch, 2009). This report presents the findings of a RCT of Fact Boxes developed for decisions related to the use of antibiotics for pneumonia and artificial hydration in advanced dementia; the DEMentia FACT box (DEMFACT) trial. The trial was conducted in the Swiss-German region of Switzerland. Physicians, relatives of dementia patients, and professional guardians were randomized to either receive (intervention) or not receive (control) the Fact Boxes. All participants were asked to make treatment decisions about antibiotics and artificial hydration

for advanced dementia patients based on hypothetical scenarios. The primary outcome was decisional conflict about treatment decisions. Secondary outcomes included knowledge about treatments, and preferences to forego antibiotics and artificial hydration.

4.2. Methods

Design

DEMFACT was a RCT conducted in the Swiss-German region of Switzerland. Participant recruitment began in April, 2016 and data collection was completed in October, 2016. The ethics commission of the canton of Zurich approved the study (KEK-ZH-No. 2015-0626). All participants provided written informed consent.

Recruitment and Randomization

To understand the impact of the DEMFACT intervention on various decision-makers, participants included physicians, relatives of dementia patients, and professional guardians who were potentially responsible for the care of advanced dementia patients. Physicians were identified from the mailing lists of the Swiss Association for Palliative Medicine, Care and Support, and the Swiss Geriatric Medicine Society. Relatives of dementia patients were identified through the Alzheimer Association of the canton of Zurich. Professional guardians were identified from the *Swiss* Association of Professional Guardians mailing list. To solicit participation, all physicians and professional guardians on the aforementioned mailing lists were sent emails in April and May of 2016, while all members of the Alzheimer Association were mailed letters in April of 2016. The emails and letters included instructions on how to contact our team if the recipient wished to participate. Participants had to be proficient in German to enroll. Individuals opting to enroll were randomly assigned by an independent statistician to either the intervention or control arm using a computer generated-

randomization list with a 1:1 allocation ratio. Randomization was stratified by participant subgroups (i.e., physicians, relatives, and professional guardians). Once randomized, participants received information about their arm assignment by mail and were asked to return a signed consent form to the research team.

Intervention

The intervention consisted of two Fact Box decision support tools for advanced dementia: one for decisions about antibiotic use and another for artificial hydration use (Center for Gerontology, University of Zurich, 2016). The structure of these tools were based on guidelines for developing Fact Boxes and incorporated guidelines from the International Patient Decision Aid Standards (Elwyn et al., 2006; McDowell et al., 2016; Schwartz et al., 2009). Their content was selected based on literature reviews conducted by two independent reviewers (AJL and SM) on the use of antibiotics and artificial hydration in advanced dementia (H. R. W. Pasman et al., 2005; 2006; van der Maaden et al., 2016; van der Steen et al., 2012). Following an iterative process, the drafts of the tools were then reviewed by the head of a dementia ward (FR), two specialists on risk communication (MMc and colleague), and eight experts on aging research (NT, SE, MMa, and colleagues). The final versions are shown in Appendices B1 and B2.

The Fact Box on antibiotics is a two-page, pocket-sized brochure that presents the typical features of pneumonia, the benefits and harms of using antibiotics, and alternative treatment options. The Fact Box on artificial hydration is a similar format and describes the administration, benefits, harms, and alternatives to artificial hydration for suspected dehydration or reduced oral intake.

Data Collection and Elements

Data collection was procedurally identical across participant subgroups, unless otherwise stated. Data were collected using two similar written questionnaires (sent and returned by mail; approximately 60 minutes to complete) completed by participants at the time of initial recruitment and one-month follow-up.

Participants in the intervention arm were mailed the Fact Boxes along with the one-month follow-up questionnaire. Participants in the control arm did not receive any additional information along with the one-month follow-up questionnaire.

The baseline and follow-up questionnaires first described two hypothetical scenarios (same scenarios at each time period). One scenario presented an advanced dementia patient with pneumonia based on a case by Mitchell et al (2015). The second scenario consisted of an advanced dementia patient with insufficient fluid intake based on a case by Garbiel and Tschanz (2015). After reading each scenario, participants were subsequently asked the same series of questions pertaining to the use of antibiotics or artificial hydration. Comfort with decision-making was assessed using a validated German version of the Decisional Conflict Scale (DCS-D; 5-point Likert scale of 16 items; range 0-100, higher scores indicate greater conflict) (Buchholz, Hölzel, Kriston, Simon, & Härter, 2011; O'Connor, 1995). Participants' knowledge was ascertained using 7-item true-false scales specific to each treatment (scored, 1=true, 0=false/don't know; range 0-7, higher scores indicate greater knowledge) (the scales are shown in Appendices B3 and B4). Preferences to use antibiotics and artificial hydration were measured using single question with response options including; 'use', 'forego', or 'undecided'.

Other participant data collected only at baseline included: demographics (age, gender, and religion (Protestant, Catholic, no religion, and other)), the educational level of relatives of dementia patients (≥ high school versus other), and whether participants had previously made a decision about the use of antibiotics and/or artificial hydration for a person with dementia. Professional guardians reported whether they had previously served as a legal guardian for a person with dementia.

In the intervention arm only, participants were asked to rate the helpfulness of the Fact Boxes ('helpful', 'somewhat helpful', 'neither helpful nor unhelpful', 'somewhat unhelpful', and 'unhelpful'); appropriateness of both the content and layout ('very good', 'good', 'fair', 'bad', and 'very bad'); and amount of information ('too much', 'too little', and 'exactly right'). The physicians were asked if they agree to using Fact Boxes while communicating with patients/decision-makers ('agree', 'somewhat agree', 'neither agree nor disagree', 'somewhat disagree', and 'disagree').

Statistical Analysis

The trial's primary outcome was the reduction in DCS-D scores for decisions on the use of antibiotics and artificial hydration. Secondary outcomes included knowledge about each treatment, and preferences to forego the treatments. Analyses were performed using R Version 3.3.2 (Boston, MA). Means with standard deviations (SDs) and frequencies described continuous and categorical variables, respectively. Outcomes were compared between trial arms at baseline using independent *t*-tests for continuous variables and chi-squared tests for categorical variables.

Similar approaches were used to analyze outcomes for decisions related to antibiotic and artificial hydration use. Linear mixed-effects models (lme4 package) were used to

examine the outcomes of DCS-D and knowledge. To capture changes between the one-month follow-up and baseline measures in the intervention relative to the control arm, these models included a term specifying the interaction between trial arms (intervention versus control) and assessments (one-month follow-up versus baseline). Random effects were used to account for repeated measurements among individuals. Unstandardized beta (b) and 95% confidence intervals (CIs) were computed. Logistic regression models compared changes in treatment preferences ('forego' versus 'use' or 'undecided') between the one-month follow-up and baseline in the intervention relative to the control arm. Odds ratios (ORs) and 95% CIs were computed. Models were generated for all participants and also stratified by participant subgroups.

A minimum sample size of 198 was calculated to provide at least 80% power to detect an effect of 0.1 between trial arms for the primary outcome. The sample size calculation assumed two repeated measurements and a 5% type I error rate. A conservative effect size was selected because the impact of decision aids on decisional conflict is highly variable (Hanson et al., 2011; Mitchell et al., 2001; Snyder et al., 2013; Volandes, Barry, Chang, & Paasche-Orlow, 2009a).

4.3. Results

Enrollment and Participant Characteristics

Of the 3860 individuals approached for participation, 254 (6.6%) contacted the research team indicating their willingness to participate, and all were eligible for recruitment (the CONSORT flow diagram of participant subgroups is shown in Appendix B5). During the course of the study, fifteen participants (intervention, N=10; control, N=5) stopped responding to e-mails and/or phone calls, and seven participants withdrew (intervention,

N=4; control, N=3). The final analytic sample completing both baseline and follow-up assessments included 232 participants (intervention, N=114; control, N=118) consisting of the following subgroups: intervention (physicians, N=30 (26.3%); relatives, N=51 (44.7%); and professional guardians, N=33 (28.9%)), and control (physicians, N=34 (28.8%); relatives, N=49 (41.5%); and professional guardians, N=35 (29.7%)).

Table 4. Baseline characteristics of participants (N=232) by trial arm

Characteristics	Intervention (N=114) No. (%)	Control (N=118) No. (%)
Participants		
Physicians	30 (26.3)	34 (28.8)
Relatives	51 (44.7)	49 (41.5)
Professional guardians	33 (28.9)	35 (29.7)
Age, year, mean ± standard deviation[a]	56.1 ± 14.1	55.0 ± 13.5
range	26–87	27–87
Female[a]	68 (59.6)	77 (65.3)
Religion[a]		
Protestant	52 (45.6)	42 (35.6)
Catholic	20 (17.5)	38 (32.2)
no religion	27 (23.7)	21 (17.8)
other	14 (12.3)	15 (12.7)
Education of relative[a]		
≥ high school	50 (98.0)	45 (91.8)
Professional guardian's experience with dementia[b]	29 (87.9)	33 (94.3)
Prior decisions on[a,c]		
antibiotics	41 (36.0)	48 (40.7)
artificial hydration	39 (34.2)	42 (35.6)

[a]*Total number of missing values by demographic characteristics: age (N=1), female (N=1), religion (N=3), education of relative (N=1), and prior decisions on antibiotics (N=2) and artificial hydration (N=2).*
[b]*Professional guardians reported whether they had previously served as a legal guardian for a person with dementia.*
[c]*Participants reported whether they had previously made a decision about the use of antibiotics and/or artificial hydration for a person with dementia.*

Baseline characteristics were similar between trial arms (Table 4). Participants' mean age was 55.6 years (range 26-87) and 62.8% (N=145/231) were female. The proportion of participants who had previously made a decision about antibiotic use varied by subgroup:

physicians, N=56/64 (87.5%); relatives, N=16/99 (16.2%); and professional guardians, N=17/67 (25.4%). The proportions of participants who had made a decision about artificial hydration use were: physicians, N=57/64 (89.1%); relatives, N=15/99 (15.2%); and professional guardians, N=9/67 (13.4%).

Decisional Conflict

Baseline decisional conflict scores were comparable between trial arms (Table 5). Relative to the control arm, participants in the intervention arm had significantly lower DCS-D scores related to decisions about antibiotics (b=-8.35, 95% CI, -12.43, -4.28) and artificial hydration (b=-6.02, 95% CI, -9.84, -2.20) at the one-month follow-up compared to at baseline. When participant subgroups were analyzed separately, DCS-D scores were significantly lower in the intervention arm, with the exception being professional guardians making decisions about artificial hydration (Table 5).

Knowledge

Baseline knowledge scores were comparable between trial arms (Table 6). Relative to the control arm, participants in the intervention arm scored significantly higher on the knowledge scales related to the use of antibiotics (b=2.24, 95% CI, 1.79, 2.68) and artificial hydration (b=3.01, 95% CI, 2.53, 3.49) at the one-month follow-up compared to at baseline. Knowledge scores were significantly higher in the intervention arm for each participant subgroup for both treatment conditions (Table 6).

Table 5. The effects of Fact Box decision support tools on participants' decisional conflict about the use of antibiotics for pneumonia and artificial hydration in advanced dementia (N=232)

	Baseline Decisional Conflict[b] *Mean ± Standard Deviation*			1 Month Decisional Conflict *Mean ± Standard Deviation*		Intervention Effect[c] *Unstandardized beta* (95% Confidence Interval)
Participants	Intervention	Control	P Value	Intervention, Review Fact Boxes	Control	
All, No.[d]	114	118		114	118	
Decisional conflict about						
Antibiotic use	38.5 ± 18.0	39.0 ± 21.1	.84	28.7 ± 16.5	37.2 ± 20.3	-8.35 (-12.43, -4.28)***
Artificial hydration use	36.4 ± 17.9	36.9 ± 20.4	.86	30.1 ± 17.8	36.0 ± 19.0	-6.02 (-9.84, -2.20)**
Physicians, No.[d]	30	34		30	34	
Decisional conflict about						
Antibiotic use	32.8 ± 12.4	29.3 ± 14.1	.30	26.0 ± 13.7	28.3 ± 12.5	-5.90 (-11.48, -0.32)*
Artificial hydration use	30.4 ± 17.0	26.5 ± 15.1	.35	25.4 ± 13.2	27.0 ± 13.2	-6.41 (-12.11, -0.65)*
Relatives, No.[d]	51	49		51	49	
Decisional conflict about						
Antibiotic use	33.5 ± 16.5	39.8 ± 24.5	.15	23.5 ± 15.9	35.9 ± 21.4	-8.02 (-14.81, -1.16)*
Artificial hydration use	33.5 ± 15.3	37.1 ± 20.9	.36	23.5 ± 14.7	33.5 ± 17.6	-8.73 (-14.42, -3.02)**
Professional Guardians, No.[d]	33	35		33	35	
Decisional conflict about						
Antibiotic use	51.2 ± 18.8	47.8 ± 17.9	.46	39.4 ± 15.2	48.1 ± 20.4	-10.96 (-19.34, -2.65)*
Artificial hydration use	45.9 ± 18.8	47.3 ± 19.4	.78	44.6 ± 17.8	46.4 ± 21.1	-1.31 (-9.60, 7.02)

[a]*The validated German version of the Decisional Conflict Scale (DCS-D), range 0-100, higher scores indicate greater conflict.*

[b]*Baseline differences were analyzed using independent t-tests or chi-squared tests for continuous or categorical variables, respectively.*

[c]*The Fact Box effects were analyzed using linear mixed effects models, which accounted for repeated measurements among individuals. *P Value < 0.05; **P Value < 0.01; and ***P Value < 0.001.*

[d]*Missing values are shown in Appendix B6.*

Table 6. The effects of Fact Box decision support tools on participants' knowledge about the use of antibiotics for pneumonia and artificial hydration in advanced dementia and on preferences to forego these interventions (N=232)

	Baseline[a] *No. (%) or Mean ± Standard Deviation*			1 Month *No. (%) or Mean ± Standard Deviation*		Intervention Effects[b]
Participants	Intervention	Control	*P Value*	Intervention, Review Fact Boxes	Control	*Unstandardized beta (95% Confidence Interval)*
All, No.[c]	114	118		114	118	
Knowledge about[d]						
Antibiotic use	3.0 ± 1.8	2.9 ± 1.7	.65	5.3 ± 1.7	3.0 ± 1.8	2.24 (1.79, 2.68)***
Artificial hydration use	2.7 ± 2.0	2.7 ± 1.8	.95	5.8 ± 1.2	2.8 ± 1.8	3.01 (2.53, 3.49)***
Preferences to forego[e]						
Antibiotic use	49 (43.4)	52 (44.8)	.93	78 (69.0)	60 (50.8)	2.29 (1.08, 4.84)*[f]
Artificial hydration use	73 (64.0)	75 (64.1)	>.99	82 (72.6)	84 (71.2)	1.07 (0.49, 2.36)[f]
Physicians, No.[c]	30	34		30	34	
Knowledge about[d]						
Antibiotic use	4.2 ± 1.5	4.6 ± 1.4	.33	6.4 ± 0.9	4.9 ± 1.5	1.90 (1.21, 2.59)***
Artificial hydration use	4.8 ± 1.1	4.4 ± 1.0	.13	6.0 ± 0.8	4.7 ± 1.2	0.94 (0.33, 1.54)**
Preferences to forego[e]						
Antibiotic use	14 (46.7)	18 (52.9)	.80	22 (73.3)	21 (61.8)	2.19 (0.51, 9.33)[f]
Artificial hydration use	26 (86.7)	25 (73.5)	.32	27 (90.0)	27 (79.4)	1.00 (0.14, 7.01)[f]
Relatives, No.[c]	51	49		51	49	
Knowledge about[d]						
Antibiotic use	2.7 ± 1.9	2.3 ± 1.3	.18	5.1 ± 1.5	2.3 ± 1.1	2.41 (1.73, 3.09)***
Artificial hydration use	2.0 ± 1.8	2.0 ± 1.6	>.99	5.9 ± 1.1	1.9 ± 1.4	4.00 (3.30, 4.70)***
Preferences to forego[e]						
Antibiotic use	31 (60.8)	25 (52.1)	.50	42 (84.0)	29 (59.2)	2.54 (0.74, 8.76)[f]
Artificial hydration use	34 (66.7)	30 (61.2)	.72	39 (78.0)	34 (69.4)	1.23 (0.36, 4.18)[f]
Professional Guardians, No.[c]	33	35		33	35	
Knowledge about[d]						
Antibiotic use	2.4 ± 1.3	2.2 ± 1.5	.67	4.6 ± 1.9	2.1 ± 1.5	2.34 (1.38, 3.30)***
Artificial hydration use	2.1 ± 1.6	2.1 ± 1.7	.95	5.6 ± 1.5	2.2 ± 1.5	3.37 (2.43, 4.32)***
Preferences to forego[e]						
Antibiotic use	4 (12.5)	9 (26.5)	.26	14 (42.4)	10 (28.6)	4.64 (0.90, 23.95)[f]
Artificial hydration use	13 (39.4)	20 (58.8)	.18	16 (48.5)	23 (65.7)	1.08 (0.27, 4.29)[f]

[a]*Baseline differences were analyzed using independent t-tests or chi-squared tests for continuous or categorical variables, respectively.*

[b]*The Fact Box effects were analyzed using linear mixed effects or logistic regression models for continuous or categorical variables, respectively. The mixed effects models accounted for repeated measurements among*

*individuals. *P Value < 0.05; **P Value < 0.01; and ***P Value < 0.001.*

[c]*Missing values are shown in Appendix B7.*

[d]*Knowledge was ascertained using 7-item true-false scales specific to the use of each treatment (scored, 1=true, 0=false/don't know; range 0-7, higher scores indicate greater knowledge). The scales and proportions of correct responses per item are shown in Appendices B3 and B4 in the supplementary data, available in Age and Ageing online.*

[e]*Preferences to use antibiotics and artificial hydration were measured using single questions with the response options: 'use', 'forego', or 'undecided'.*

[f]*Unstandardized beta for categorical variables were transformed into odds ratios.*

Preferences to Forego Interventions

Baseline decisions on antibiotic use were comparable between trial arms and distributed as follows (Table 6): N=80/229 (34.9%); forego, N=101/229 (44.1%); and undecided, N=48/229 (21.0%). Baseline decisions on artificial hydration use were also comparable and had the following distribution: use, N=46/231 (19.9%); forego, N=148/231 (64.1%); and undecided, N=37/231 (16.0%).

Relative to the control arm, participants who received the Fact Box in the intervention arm were significantly more likely to prefer to forego antibiotics (OR, 2.29, 95% CI, 1.08, 4.84) at the one-month follow-up compared to at baseline. The intervention did not significantly impact preferences to forego artificial hydration, and treatment preferences did not differ when analyzed separately in each subgroup.

Acceptability of Fact Boxes

Among intervention participants, 86.8% (N=99/114) and 75.4% (N=86/114) found the Fact Boxes to be 'helpful' or 'rather helpful', respectively. Most participants rated the content as 'very good' or 'good' (antibiotics, N=79/112 (70.5%); artificial hydration, N=76/112 (67.9%)). Similarly, most participants positively rated the layout (antibiotics, N=91/113 (80.5%); artificial hydration, N=88/113 (77.9%)). While 64.3% (N=72/112) of participants rated the amount of information in both Fact Boxes as 'exactly right', 34.8% (N=39/112) and

33.9% (N=38/112) found the information to be 'too little' in the antibiotic and artificial hydration Fact Boxes, respectively. All but one physician (N=29/30, (96.7%)) were agreeable to using Fact Boxes in practice (agree, N=16/30 (53.3%); somewhat agree, N=13/30 (43.3%)).

4.4. Discussion

In this RCT, participants who received Fact Box decision support tools in the intervention arm showed significantly less decisional conflict about the use of antibiotics for pneumonia and artificial hydration in advanced dementia at the one-month follow-up compared to at baseline and relative to participants in the control arm. Fact Box recipients also showed greater knowledge about the use of these treatments and were more likely to prefer to forego antibiotics. However, the intervention did not impact preferences to withhold artificial hydration. Most users rated the Fact Boxes positively on helpfulness, content, layout, and length, and 97% of physicians stated that they would use them as a communication tool.

This RCT builds upon limited prior research examining the effects of decision support tools in advanced dementia (Einterz et al., 2014; Hanson et al., 2011; 2017; Mitchell et al., 2001; Snyder et al., 2013; Volandes, Barry, Chang, & Paasche-Orlow, 2009a; Volandes, Paasche-Orlow, Barry, Gillick, Minaker, et al., 2009b). The findings corroborate the beneficial impact of these instruments on reducing decisional conflict (Hanson et al., 2011; Mitchell et al., 2001; Snyder et al., 2013; Volandes, Barry, Chang, & Paasche-Orlow, 2009a). Furthermore, the reduction on decisional conflict we observed with our brief tool was similar to that of a more intense 20-minute decision support tool (Hanson et al., 2011). Compared to video-based supports,(Einterz et al., 2014; Hanson et al., 2017; Volandes, Barry, Chang, &

Paasche-Orlow, 2009a; Volandes, Paasche-Orlow, Barry, Gillick, Minaker, et al., 2009b) Fact Boxes are brief, handy, inexpensive, and easier to incorporate into real-life care settings.

Fact Boxes are unique in that they can be used by a variety of decision-makers, such as physicians, relatives of dementia patients, and professional guardians. This is evident by our findings that decisional conflict and knowledge improved in all of these different groups, compared to other tools designed for only one category of decision-makers (Einterz et al., 2014; Hanson et al., 2011; Mitchell et al., 2001; Snyder et al., 2013; Volandes, Barry, Chang, & Paasche-Orlow, 2009a). All but one physician (N=29/30) were agreeable to using Fact Boxes in practice, which is consistent with a prior study demonstrating the appeal of brief decision support tools to physicians (Giguere et al., 2015). Our findings that Fact Boxes aided professional guardians is particularly notable because it was relatively unknown what type of decision support they would benefit from when making end-of-life choices for patients (A. B. Cohen et al., 2015). The finding that one Fact Box impacted preferences to forego antibiotics is also noteworthy, as it suggests comfort-focused care can be promoted by a less time intensive decision support tool than previously identified (Einterz et al., 2014; Hanson et al., 2011; 2017; Volandes, Barry, Chang, & Paasche-Orlow, 2009a; Volandes, Paasche-Orlow, Barry, Gillick, Minaker, et al., 2009b).

Several limitations merit discussion. First, our recruitment process resulted in lower participation rates than studies that recruited from medical institutions (Hanson et al., 2011; Mitchell et al., 2001). Therefore, our findings cannot be generalized to eligible non-participants. Second, generalizability is also limited to the Swiss-German region of Switzerland and to hypothetical decisions. The effect of the intervention may vary in other regions and in real-world situations. Lastly, the statistical power may have been insufficient

to detect significant differences in subgroups (e.g., decisional conflict about artificial hydration use in professional guardians) and secondary outcomes (e.g., preferences to forego artificial hydration).

In this RCT, Fact Box decision support tools reduced participants' decisional conflict in hypothetical scenarios about the use of antibiotics for pneumonia and artificial hydration in advanced dementia. Both Fact Boxes increased participants' knowledge about each treatment and the Fact Box on antibiotics led to an increase in preferences to withhold this intervention. Through improving the quality of decision-making for a variety of decision-makers, potentially promoting less aggressive care, and providing physicians with a useful communication tool, Fact Boxes may be a promising decision support tool for real-world settings.

5. Study 3: Perceptions about Controversial End-of-Life Practices

Physician and Surrogate Agreement with Assisted Dying and Continuous Deep Sedation in Advanced Dementia in Switzerland[3]

5.1. Introduction

Dementia afflicts more than 50 million people worldwide and is one of the most common causes of death in Switzerland, and worldwide (Federal Statistical Office FSO, 2017; World Health Organization, 2015a). In advanced dementia, patients have profound cognitive and functional deficits and experience clinical complications that may cause discomfort and a poor quality of life (Hendriks et al., 2014; Mitchell et al., 2009; van der Steen et al., 2016).

Assisted dying is a controversial practice that has been used in certain contexts among patients with life-limiting disease (E. J. Emanuel et al., 2016). Assisted dying is when a physician either administers drugs that cause a person to die (i.e., euthanasia) or provides lethal drugs for self-administration (i.e., physician-assisted suicide) (Radbruch et al., 2016). To date, physician-assisted dying is legal in only a few states in the United States and a limited number of countries, including Switzerland (E. J. Emanuel et al., 2016; Li et al., 2017). However, only the Netherlands, Belgium, and Luxembourg allow assisted dying for people with advanced dementia (Neil, 2016). This request must be made in an advanced directive by a patient with dementia when decision-making capacity is still intact. Only

[3] A similar version of this chapter is currently being prepared for publication (Loizeau, Cohen, Mitchell, Theill, Eicher, Martin, & Riese).

limited research exists on the perceptions of physicians and surrogates about the use of assisted dying in advanced dementia (Bolt et al., 2015; Kouwenhoven et al., 2015; Tomlinson et al., 2015; Tomlinson & Stott, 2014).

Another controversial practice for terminally ill patients is continuous deep sedation until death (CDS). This is an intensive palliative practice that is used as a last resort to alleviate suffering (Miccinesi et al., 2006; Ziegler et al., 2018). Medications are administrated until death to lower the level of consciousness and relieve refractory symptoms of patients with a life expectancy of typically less than two weeks (Cherny et al., 2009). To date, CDS has predominantly been used among advanced cancer patients who experience extreme physical suffering in their final weeks of life (McCarthy et al., 2000; Miccinesi et al., 2006). CDS has rarely been used in advanced dementia, a condition predominantly characterized by cognitive impairments with some, but typically less, physical suffering than metastatic cancer (Anquinet et al., 2013; Hendriks et al., 2014; van der Steen et al., 2016).

To better understand the perceptions of physicians and surrogates about the use of assisted dying and CDS in advanced dementia, we analyzed baseline data from a randomized controlled trial (RCT), the DEMentia FACT box (DEMFACT), conducted in the Swiss-German region of Switzerland. The objectives of this report were to: 1) describe physician and surrogate agreements with the use of assisted dying and CDS in advanced dementia, and 2) compare the agreements with the use of these practices in these two groups.

5.2. Methods

Data source

Data were drawn from baseline assessments ascertained in the DEMFACT study conducted between June, 2016 and October, 2016 in the Swiss-German region of

Switzerland. DEMFACT was a RCT that evaluated FACT box decision-support tools for treatment decisions in advanced dementia among 64 physicians and 168 surrogates (relatives of dementia patients, N=100; professional guardians, N=68) who were randomized to either the intervention (N=114) or control arm (N=118) (Loizeau et al., n.d.). Intervention and control arm participants were mailed written questionnaires at baseline and one month later that asked questions about the use of treatments for advanced dementia patients based on hypothetical scenarios. At the one-month follow-up, intervention participants received the decision support tools, whereas control participants were given no additional information.

The main DEMFACT study compared changes in pre-specified outcomes between the baseline and follow-up assessments in the intervention arm relative to the control arm. In this report, combined data from the baseline questionnaires in both arms (i.e., before receiving the decision support tools in the intervention arm) were analyzed to describe agreements with the use of continuous sedation and assisted dying in advanced dementia. Baseline questionnaires were completed between June 2, 2016 and July 31, 2016. The ethics commission of the canton of Zurich approved the study's conduct (KEK-ZH-No. 2015-0626). All participants provided written informed consent.

Population

To understand the impact of the DEMFACT intervention on various decision-makers, participants included physicians and surrogates (relatives of dementia patients and professional guardians) who were potentially responsible for the care of advanced dementia patients. Physicians were identified from the mailing lists of the Swiss Association for Palliative Medicine, Care and Support, and the Swiss Geriatric Medicine Society. Surrogates were identified either through the Alzheimer Association of the canton of Zurich or from the

Swiss Association of Professional Guardians mailing list. The detailed recruitment procedure is described elsewhere (Loizeau et al., n.d.). Eligible participants were mailed a consent form, which they were asked to sign and return to the research team.

Data Elements

Data collection was procedurally identical across physician and surrogate participants. All variables in this report were collected at the DEMFACT baseline assessment using a written questionnaire sent and returned by mail (approximately 60 minutes to complete).

The outcomes were participants' agreement with the use of assisted dying and CDS in advanced dementia. Agreements with assisted dying were ascertained using the following question: 'The current legislation prohibits physician-assisted suicide (assisted dying) for persons lacking the capacity to consent. This prevents persons with advanced dementia from accessing the services of assisted dying organizations. Independent of the current legal situation, would you personally support the use of assisted suicide (one form of physician-hastened death) for persons with advanced dementia?' Perceptions about the use of CDS were measured using the following question: 'At the end of life, it is possible to use medications, administered until death, to relieve the symptoms of a person with advanced dementia and put them into a permanent, artificial sleep (continuous sedation). Would you personally support the use of continuous sedation for persons with advanced dementia?' For both questions, participants were asked to select one of the following response options: 'completely agree', 'somewhat agree', 'somewhat disagree', 'completely disagree', or 'do not know'.

Other participant data ascertained at baseline included: demographics (age, gender, nationality (Swiss, German, and other), religion (Protestant or Catholic, other religion, no

religion, and refused to answer), and educational level (≥ high school versus other)); and whether participants had previously made a decision about the use of antibiotics and/or artificial hydration for a person with advanced dementia.

Analysis

Analyses were performed using R Version 3.3.2 (Boston, MA). Means with standard deviations (SDs) and frequencies described continuous and categorical variables, respectively.

Logistic regression was used to examine the association between decision-maker type (surrogate versus physician) and agreement with the following practices in advanced dementia (outcomes); 1. assisted dying and 2. CDS. For each practice, the outcome was dichotomized as 'agree' (i.e., 'completely agree' and 'somewhat agree') versus 'disagree' (i.e., 'completely disagree' and 'somewhat disagree'), and excluded 'do not know' responses. Covariates considered a priori to be possibly associated with supporting the use of assisted dying or CDS,(Tomlinson & Stott, 2014) included: participant demographic characteristics (age (dichotomized at median), gender, and religion (dichotomized as no religion versus any, excluding 'refused to answer')); and prior decisions about the use of antibiotics and/or artificial hydration in advanced dementia (dichotomized as no prior major treatment decision versus any). Bivariable analyses examined the unadjusted associations between each covariate and the outcome. Variables associated with the outcome at $P < 0.10$ in the unadjusted analyses were entered into a multivariable model. The final adjusted model included those variables significantly associated with the outcome at $P < 0.05$. Adjusted odds ratios (ORs) with 95% Confidence Intervals (CIs) were computed.

5.3. Results

Subject Characteristics

Of the 3860 individuals approached for participation, 254 (6.6%) contacted the research team indicating their willingness to participate, and all were eligible for enrollment. Prior to study completion, 15 (5.9%) participants stopped responding to e-mails and/or phone calls (physicians, N=9/74 (12.2%); surrogates, N=6/180 (3.3%)) and 7 (2.8%) participants withdrew (physicians, N=1/74 (1.4%); surrogates, N=6/180 (3.3%)). The final sample size included the remaining 64 physicians and 168 surrogates.

Table 7. Physician and Surrogate Characteristics (N=232)

Characteristics	Physicians (N=64), *No. (%)*	Surrogates (N=168), No. (%)
Age, mean ± standard deviation[a]	50.6 ± 9.9	57.4 ± 14.6
Age > 55 (median)	21 (32.8)	91 (54.5)
Female[a]	30 (46.9)	115 (68.9)
Nationality		
Swiss	44 (72.1)	157 (94.6)
German	13 (21.3)	7 (4.2)
Other	4 (6.6)	2 (1.2)
Religion[a]		
Protestant or catholic	44 (68.8)	108 (65.5)
Other	9 (14.1)	11 (6.7)
No religion	10 (15.6)	38 (23.0)
Refused to answer	1 (1.6)	8 (4.8)
Education		
≥ high school	64 (100)	161 (97.0)
Any prior major treatment decision in dementia[a,b]	58 (90.6)	42 (25.3)

[a]*The total number of missing values by characteristic was: age, N=1; female, N=1; nationality, N=5; education, N=2; religion, N=3; and any prior major treatment decision, N=2.*
[b]*Decision-makers reported whether they had or had not previously made any major decision about the use of antibiotics and/or artificial hydration for a person with advanced dementia.*

The baseline characteristics of the physicians and surrogates are shown in Table 7. The physicians' mean (SD) age was 50.6 (9.9) years, 46.9% (N=30/64) were women, and

72.1% (N=44/61) were Swiss. The surrogates' mean (SD) age was 57.4 (14.6) years, 68.9% (N=115/167) were women, and 94.6% (N=157/166) were Swiss. A total of 68.8% (N=44/64) of physicians and 65.5% (N=108/165) of surrogates reported being either Protestant or Catholic. A total of 90.6% (N=58/64) of physicians had previously made a major treatment decision for a person with advanced dementia, whereas only 25.3% (N=42/166) surrogates had ever made such a decision.

Agreement with Assisted Dying

The distribution of physician responses about the use of assisted dying in advanced dementia was as follows: completely agree, 4.7% (N=3/64); somewhat agree, 15.6% (N=10/64); somewhat disagree, 26.6% (N=17/64); completely disagree, 50.0% (N=32/64); and do not know, 3.1% (N=2/64). The distribution among surrogates was: completely agree, 20.2% (N=34/168); somewhat agree, 26.8% (N=45/168); somewhat disagree, 23.2% (N=39/168); completely disagree, 22.6% (N=38/168); and do not know, 7.1% (N=12/168).

In the unadjusted analyses, participant variables associated with agreement with assisted dying at a $P < 0.10$ were: age > 55 years; any prior major treatment decision in dementia; and being a surrogate (versus a physician) (Table 8). After multivariable adjustment, only being a surrogate (versus a physician) remained significantly associated with a higher likelihood of agreeing with the use of assisted dying (adjusted OR, 3.87; 95% CI, 1.94, 7.69).

Table 8. Association between decision-maker type and agreement with the use of assisted dying in advanced dementia[a]

Characteristic	Total No. (%) of Decision-Makers with Characteristic (N=218)	No. (%) of Decision-Makers Agreeing with Assisted Dying (N=92)		Odds Ratio[b] for Agreement with Assisted Dying (95% Confidence Interval)	
		With Characteristic Present	With Characteristic Absent	Unadjusted	Adjusted
Surrogates (versus physicians)	156 (71.6)	79 (36.2)	13 (6.0)	3.87 (1.94, 7.69)[e]	3.87 (1.94, 7.69)
Covariates					
Age > 55 (median)[c]	106 (48.8)	54 (24.9)	38 (17.5)	1.99 (1.15, 3.45)[e]	
Female[c]	133 (61.3)	62 (28.6)	30 (13.8)	1.57 (0.90, 2.76)	
No religious affiliation (versus any)[c]	45 (21.4)	24 (11.4)	67 (31.9)	1.67 (0.86, 3.24)	
Any prior major treatment decision in dementia[d]	97 (44.9)	29 (13.4)	61 (28.2)	0.41 (0.23, 0.71)[e]	

[a]*Decision-makers were 42.2% (N=92/218) agreeing with the use of assisted dying in advanced dementia.*
[b]*Logistic regression was used in all analyses, and unadjusted and adjusted odds ratio were computed.*
[c]*The total number of missing values was: age, N=1; female, N=1; no religion, N=8 (missing values, N=3; refused, N=5); and any prior major treatment decision, N=2.*
[d]*Decision-makers reported whether they had or had not previously made any major decision about the use of antibiotics and/or artificial hydration for a person with advanced dementia.*
[e]*Variables that were significant at P < 0.10 in bivariable analyses and entered into the multivariable model.*

Agreement with Continuous Deep Sedation

The distribution of physician responses about the use of CDS in advanced dementia was as follows: completely agree, 20.3% (N=13/64); somewhat agree, 31.3% (N=20/64); somewhat disagree, 31.3% (N=20/64); completely disagree, 6.3% (N=4/64); and do not know, 10.9% (N=7/64). The distribution among surrogates was: completely agree, 12.6% (N=21/167); somewhat agree, 29.3% (N=49/167); somewhat disagree, 28.7% (N=48/167); completely disagree, 18.6% (N=31/167); and do not know, 10.8% (N=18).

The only covariate associated with a greater likelihood of supporting the use of CDS at a $P \leq 0.10$ was no religion (versus any) (Table 9). After adjusting for religion, being a

surrogate (versus a physician) was not significantly associated with agreement with the use of CDS (AOR, 0.69; 95% CI, 0.36, 1.29).

Table 9. Association between decision-maker type and agreement with the use of continuous deep sedation in advanced dementia[a]

Characteristic	Total No. (%) of Decision-Makers with Characteristic (N=206)	No. (%) of Decision-Makers Agreeing with Continuous Deep Sedation (N=103)		Odds Ratio[b] for Agreement with Continuous Deep Sedation (95% Confidence Interval)	
		With Characteristic Present	With Characteristic Absent	Unadjusted	Adjusted
Surrogates (versus physicians)	149 (72.3)	70 (34.0)	33 (16.0)	0.64 (0.35, 1.19)	0.69 (0.36, 1.29)[f]
Covariates					
Age > 55 (median)[c]	101 (49.3)	55 (26.8)	48 (23.4)	1.39 (0.81, 2.42)	
Female[c]	128 (62.4)	64 (31.2)	39 (19.0)	0.97 (0.55, 1.71)	
No religion (versus any)[c]	41 (20.9)	27 (13.8)	74 (37.8)	2.11 (1.03, 4.33)[e]	2.19 (1.06, 4.51)
Any prior major treatment decision in dementia[d]	88 (43.1)	47 (23.0)	55 (27.0)	1.27 (0.73, 2.22)	

[a]*Decision-makers were 50.0% (N=103/206) agreeing with the use of continuous deep sedation in advanced dementia.*
[b]*Logistic regression was used in all analyses, and unadjusted and adjusted odds ratio were computed.*
[c]*The total number of missing values was: age, N=1; female, N=1; no religion, N=10 (missing values, N=2; refused, N=8); and any prior major treatment decision, N=2.*
[d]*Decision-makers reported whether they had or had not previously made any major decision about the use of antibiotics and/or artificial hydration for a person with advanced dementia.*
[e]*The only variable that was significant at P < 0.10 in bivariable analyses and entered into the multivariable model.*
[f]*After adjusting for religion, the association between being a physician and supporting the use of continuous deep sedation until death remained not significant.*

5.4. Discussion

In this report, a minority of physicians (20%) and about half of surrogates (47%) supported the use of assisted dying for patients with advanced dementia. Surrogates were significantly more likely to agree with the use of this practice than physicians. About half of physicians (52%) and a slightly lower proportion of surrogates (42%) agreed with the use of CDS for these patients, which was not a significant difference between groups.

This study confirms and furthers limited existing research on the perceptions of physicians and surrogates about assisted dying in advanced dementia (Bolt et al., 2015; Kouwenhoven et al., 2015; Tomlinson et al., 2015; Tomlinson & Stott, 2014). The use of assisted dying has increased in countries where it is legal (the Netherlands and Belgium) over the last decade, but much less frequently for patients with dementia compared to those with terminal illnesses that do not impact decision-making abilities (Dierickx et al., 2017; E. J. Emanuel et al., 2016; Neil, 2016). Prior research has shown that most physicians are opposed to the use of this practice in dementia (Bolt et al., 2015; Kouwenhoven et al., 2015; Tomlinson & Stott, 2014). Regardless of the presence of an advance directive, physicians are reluctant to perform physician-assisted suicide for patients lacking decision-making capacity (Kouwenhoven et al., 2015). A Dutch study of 1456 physicians found that physicians were more willing to perform assisted dying for cancer patients with intact cognition (85%) than for advanced dementia patients who requested euthanasia in an advance directive prepared when they were still capable of making medical decisions (33%) (Bolt et al., 2015). One chief concern is that preferences change over time,(E. J. Emanuel et al., 2000) and that patients who imagine a future state with advanced dementia as one not worth living, once in that state, they may appear to still retain a desire to live. Although surrogates may share this concern, their more favorable view of the use of assisted dying may be driven by a relatively greater aversion to their loved one experiencing the poor quality of life, suffering, and indignities of advanced dementia (Tomlinson et al., 2015; Tomlinson & Stott, 2014). The greater likelihood of surrogates agreeing to assistance in dying is that their participation, unlike physicians, is not required to complete the act.

Our findings build on the very limited data on the use of CDS in advanced dementia,(Anquinet et al., 2013; Hendriks et al., 2014) and reveal that there is no consensus

among either physicians or surrogates about the appropriateness of using CDS in this population. This finding corroborates qualitative research showing that both groups of key decision-makers have mixed feelings about the use of this practice among terminally ill patients (Bruinsma, Rietjens, Seymour, Anquinet, & van der Heide, 2012; Ziegler, Merker, Schmid, & Puhan, 2017). To date, CDS has predominantly been used and studied in advanced cancer, a condition where decision-making capacity remains intact and the dying process is most commonly accompanied by intractable physical pain and suffering (McCarthy et al., 2000; Miccinesi et al., 2006). In contrast to these patients, advanced dementia patients cannot participate in decision-making or report the source of their discomfort due to their serious cognitive impairments (van der Steen et al., 2016). Although pain is generally under-detected and under-treated in advanced dementia, physical suffering is not the primary symptom of this condition, unlike metastatic diseases (McCarthy et al., 2000; Morrison & Siu, 2000a). It also may be challenging for physicians to assess the intensity of a patient's suffering, making it difficult to justify the use of CDS in advanced dementia. Furthermore, pain and agitation in advanced dementia are often caused by other medical complications, such as infections, and may be effectively controlled with standard palliative medications (Hendriks et al., 2014; Mitchell et al., 2009).

This study has several limitations that merit discussion. First, our participation rate was low and thus our findings cannot be generalized to eligible non-participants. Second, generalizability is also limited to the Swiss-German region of Switzerland and to hypothetical situations. The perceptions about end-of-life practices may vary in other regions of Switzerland and in real-life situations. Third, the questions may not have been detailed enough to detect nuances in participants' perceptions (Magelssen, Supphellen, Nortvedt, & Materstvedt, 2016). It is likely that participants' opinions would have been different if they

were given more information, such as a statement indicating the patient made a written request for assisted dying before losing decision-making capacity. Lastly, the statistical power may have been insufficient to detect significant differences in secondary outcomes, notably differences in perceptions about CDS.

This study expands upon the limited existing literature on the perceptions of physicians and surrogates about the use of assisted dying and CDS in patients with advanced dementia. Physicians were more opposed to the use of assisted dying than surrogates, and about half of participants in both groups perceived CDS as an appropriate option in advanced dementia. In general, there is a clear need to improve end-of-life care in this patient population. However, due to the pratical, ethical, and legal issues associated with performing assisted dying and CDS for patients who lack decision-making capacity, it remains unclear whether these practices would help accomplish this goal.

6. General Discussion

This thesis aimed to advance our understanding of and improve medical decision-making in advanced dementia among various decision-makers by examining associations between decision-making supports and health outcomes in both decision-makers and patients. Findings from studies 1, 2, and 3 inform decision-making and are illustrated in Figure 3 using an extension of the Quality of Care model by Donabedian (Donabedian, 1988; Teno et al., 1997).

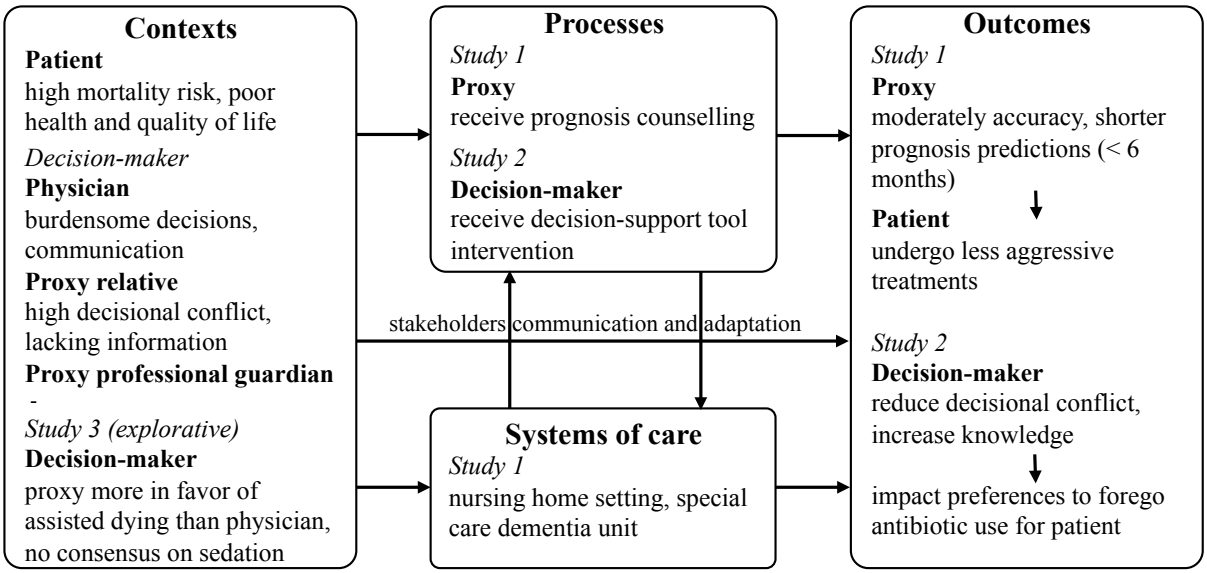

Figure 3. Contribution of studies 1-3 illustrated using the Quality of Care Model

All studies corroborated and went beyond the extant research landscape on burdensome *contexts* of decision-making (Engel, Kiely, & Mitchell, 2006; Givens et al., 2009; Pautex et al., 2013; You et al., 2015). Studies 1 and 2 identified the positive impact of proxy counseling and decision-supports (*processes*) on *outcomes* in both decision-makers (studies 1 and 2) and patients (study 1 only). Study 3 provides novel insights into decision-makers' mixed perceptions about controversial end-of-life practices.

6.1. Summary of Findings

Study 1 determined the accuracy of proxies' prognostic estimates for nursing home residents with advanced dementia, identified factors associated with those estimates, and examined the association between their estimates and use of burdensome interventions. Data were combined from two studies that prospectively followed 764 residents with advanced dementia and their proxies in Boston area nursing homes for 12 months: 1. The Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia, conducted from September 2009 to November 2012 (362 resident/proxy dyads; 35 facilities); and 2. The Educational Video to Improve Nursing Home Care in End-stage Dementia conducted from March 2013 to July 2017 (402 resident/proxy dyads; 62 facilities). During quarterly telephone interviews, proxies stated whether they believed the resident would live less than 1 month, 1 to 6 months, 7 to 12 months, or more than 12 months. Prognostic estimates were compared with resident survival. Resident and proxy characteristics associated with proxy prognostic estimates were determined. Furthermore associations between prognostic estimates and whether residents experienced any of the following were also determined: hospital transfers, parenteral therapy, tube feeding, venipunctures, and bladder catheterizations. Findings showed that proxies of nursing home residents with advanced dementia predicted how long the resident would live with moderate accuracy. Having been asked about their opinion about the goals of care was the factor most strongly associated with the proxies' perception that the resident had less than 6 months to live. Residents were significantly less likely to experience burdensome interventions when their proxies perceived they would die within 6 months. These findings suggest that proxies are reasonably good at estimating when residents with advanced dementia will die and their prognostic perceptions may influence the type of care the resident receives.

Study 2 tested the impact of Fact Box decision support tools on decisional conflict, knowledge, and preferences about the use of antibiotics and artificial hydration in advanced dementia. The DEMentia FACT box (DEMFACT) was a randomized controlled trial that followed 232 participants (intervention, 114; control, 118) (64 physicians, 100 relatives of dementia patients, 68 professional guardians) in the Swiss-German region of Switzerland. Participants received written questionnaires at baseline and one month later in which they were asked questions about hypothetical treatment scenarios. Intervention participants received Fact Box decision support tools (two-page, pocket-sized brochures) on antibiotics for pneumonia and artificial hydration in advanced dementia at the one-month follow-up. The primary outcome was change in decisional conflict (DCS-D; range 0<100) about treatment decisions. Secondary outcomes included knowledge about treatments (range 0<7) and preferences to forego treatments. Findings showed that participants who received Fact Box decision support tools in the intervention arm showed significantly less decisional conflict about the use of antibiotics for pneumonia and artificial hydration in advanced dementia at the one-month follow-up compared to at baseline and relative to participants in the control arm. Fact Box recipients also showed greater knowledge about the use of these treatments and were more likely to prefer to forego antibiotics. However, the intervention did not impact preferences to withhold artificial hydration. Most users rated the Fact Boxes positively on helpfulness, content, layout, and length, and 97% of physicians stated that they would use them as a communication tool. These findings suggest that Fact Box decision support tools reduced decisional conflict, increased knowledge, and promoted preferences to forego antibiotics in advanced dementia among various decision-makers.

Study 3 described and compared physician and proxy perceptions about the use of assisted dying and continuous deep sedation until death in advanced dementia. Sixty-four

Physicians and 168 proxies of persons with advanced dementia were recruited as part of the aforementioned DEMFACT study. At baseline, all participants were asked about the extent to which they would agree with the use of assisted dying and continuous deep sedation in advanced dementia patients using the following response options: completely agree, somewhat agree, somewhat disagree, completely disagree, or do not know. Multivariable logistic regression models compared the likelihood of agreement with these practices between proxies and physicians. Findings showed that a total of 20% of physicians and 47% of proxies agreed with assisted dying in advanced dementia. Proxies were significantly more likely to agree with this practice compared to physicians. Regarding to continuous deep sedation, 52% of physicians and 42% of proxies agreed with this practice, which did not differ significantly between groups. Therefore, these findings suggest that proxies were more likely to consider assisted dying in advanced dementia than physicians, and about half of participants in both groups reported continuous deep sedation to be an appropriate option for this population.

6.2. Goals of Care Discussions as a Resource for Decision-Making

Goals of care discussions, or proxy counseling in general, can positively influence end-of-life care (Givens et al., 2018; Hanson et al., 2017; Mitchell et al., 2009; 2017; van der Steen et al., 2013). Of the 2526 proxy interviews (cohort of 764 proxies of patients with advanced dementia) in study 1, proxies reported having had a goals of care discussion in only 45% of interviews. This finding is in line with prior research showing that although these conversations can promote better care decisions, they are not always conducted in long-term care settings (Givens et al., 2009; 2018; Hanson et al., 2017).

Goals of care discussions are, per definition, optimal to discuss the patient's goals of care. In study 1, proxies who had been asked by a physician about their opinion regarding the goal of care were more likely to perceive that the resident had less than 6 months to live. This perception was in turn associated with a lower likelihood that the resident experienced burdensome interventions. Although we do not know the specific content of the goals of care discussions, these discussions seem to play a crucial role in making proxies understand the terminal condition of advanced dementia, and thus in promoting comfort care instead of intensive care. Because most proxies are unaware of the poor prognosis in advanced dementia, they are very likely to make biased treatment decisions (Mitchell, Kiely, & Hamel, 2004a; van der Steen et al., 2013). For example, if the proxy thinks that the patient will live longer than 12 months, the proxy may be more inclined to choose curative medications such as antibiotics. A more accurate perception about the poor prognosis in advanced dementia is therefore crucial for delivering goal-directed care. In this regard, our findings confirm that proxy perception of prognosis influence end-of-life care and expand on this notion by suggesting that goals of care discussions could play a role in this relationship.

Goals of care discussions can help promote high-quality decision-making and goal-directed care. But what exactly are the necessary attributes of a goals of care discussion for it to improve decision-making? According to the judgment and decision-making literature, available choice options are weighed by the decision-maker in order to subsequently select the option with the highest expected value (Rangel et al., 2008). In the context of treatment decisions on behalf of others, a decision-maker clearly needs to know all choice options before he can objectively maximize expected value. To subsequently and accurately represent the expected value of a given choice option in their value function, decision-makers need to incorporate information about the patient's health as precisely as possible. Based on our study

and the existing literature, it is important for decision-makers to understand the following aspects of advanced dementia in order to make informed decisions: 1. terminal condition of dementia; 2. expected re-occurrence of complications; 3. benefit-to-harm ratio about treatment administration; 4. benefit-to-harm ratio about treatment effects; and 5. alternative to treatments. With this information in mind, proxies can coordinate with physicians to weigh goals of care options such as to prolonging life, maintaining functions or maximizing comfort in accordance with the patient's preferences, if available (Mitchell et al., 2017; van der Steen et al., 2014). Going through those decision-making steps during a goals of care discussion can result in improved outcomes for both the decision-maker and the patient.

Based on the WHO's definition of *Healthy Ageing* as *the process of developing and maintaining the functional ability that enables well-being in older age* (page 28), one might be inclined to deduce that *well-being* is defined by health in a classical and strict sense (World Health Organization, 2015b). While this deduction may be correct in certain situations, in the case of critical and terminal illnesses where alleviating pain completely is no longer an option, the concept of *well-being* may be accurately thought of as the individuals' ability *to be and to do what they have reason to value* (p. 28; World Health Organization, 2015b). In those cases, *well-being* can thus be interpreted to result from decisions that are made in accordance with end-of-life preferences. In advanced dementia, however, patients lack decision-making capacity and their *well-being* completely depends on the decision-maker's ability to make decisions in line with their preferences. Because goals of care discussions can promote this process, they are a resource for high-quality decision-making and a means by which decision-makers and patients can experience *well-being* and in turn *healthy ageing*.

6.3. Decision Support Tools as a Resource for Decision-Making

Decision support tools in advanced dementia can foster communication between decision-makers and result in better outcomes for both the decision-maker and patient (Einterz et al., 2014; Hanson et al., 2017; Volandes, Barry, Chang, & Paasche-Orlow, 2009a; Volandes, Paasche-Orlow, Barry, Gillick, Minaker, et al., 2009b). Although these tools have been found to be effective, most are videos tailored to only a single group of decision-maker.

Fact Boxes on the use of antibiotics and artificial hydration in advanced dementia are brief, handy, inexpensive, easier to incorporate into real-life care settings and tailored to various decision-makers. In study 2, Fact Box decision support tools reduced decisional conflict in hypothetical scenarios, increased knowledge, and promoted preferences to forego antibiotics in advanced dementia among various decision-makers. These findings suggest that simple Fact Boxes may be as effective as other more intensive tools in supporting decision-making, and this not only in one single group of decision-makers but in various decision-makers (Einterz et al., 2014; Hanson et al., 2017; Volandes, Barry, Chang, & Paasche-Orlow, 2009a; Volandes, Paasche-Orlow, Barry, Gillick, Minaker, et al., 2009b). The fact that all decision-makers have increased their knowledge after reviewing the Fact Box suggests that all understood the provided information the same way. A prior study has shown that even after proxy counseling by physicians, both parties had different perceptions about the content of their conversations (D. B. White et al., 2016a). In the specific case of decision-making on behalf of someone else, it is particularly important that all involved decision-makers are on the same page. By providing similar, easily understandable, standardized information to various decision-makers, Fact Boxes could have the potential to reduced communication bias between these decision-makers.

This thesis investigated decision-making not only in relatives as most commonly in advanced dementia research but also in physicians. Study 2 found that Fact Boxes increased the knowledge of physicians about the use of antibiotics and increased preferences to forego antibiotics. The misuse of antibiotics by physicians among patients with advanced dementia is extensive and antimicrobial overuse causes the development of MDROs, a public health threat and worldwide concern (Ho et al., 2010; Mitchell et al., 2014; World Health Organization, 2014b). In this regard, by promoting a better physician understanding about the use of antibiotics in advanced dementia, simple Fact Boxes could potentially reduce the misuse of antibiotics and contribute to measures taken against the development of MDROs in frail patients.

This thesis also spotlights the population of professional guardians. With an ageing global demographic, more patients with advanced dementia will have no family members available to make medical decisions on their behalf and thus decision-making by professional guardians will become even more likely (A. B. Cohen et al., 2015). Findings from study 2 revealed the high decisional conflict of professional guardians about treatment decisions in advanced dementia and lack of knowledge, suggesting that this population would benefit from increased support. To date, most research on advanced dementia does not differentiate their outcomes from the ones of family decision-makers. Research should further explore their decision-making and subjective experience when they have neither physicians' medical expertise nor relatives' insights about patients' history to draw from.

In addition to addressing the needs of various decision-makers, this thesis sought to develop decision-support tools that could be easily implemented in busy and complex medical settings. Compared to other video decision support tools,(Einterz et al., 2014;

Hanson et al., 2017; Volandes, Barry, Chang, & Paasche-Orlow, 2009a; Volandes, Paasche-Orlow, Barry, Gillick, Minaker, et al., 2009b) Fact Boxes are brief and handy; a format that could be more easily implemented and suitable to be used in direct communication. A prior randomized clinical trial in North-Carolina among 302 residents with advanced dementia and their family decision-makers has found that a goals of care video decision aid followed by a structured discussion improved end-of-life communication and enhance palliative care plans (Hanson et al., 2017). The video format in this trial did not allow using the decision support as direct communication tool. However, it seems that the most difficult challenge and barrier for decision-making is *finding adequate language* to transfer medical knowledge and discuss end-of-life preferences (Givens et al., 2009; 2012; Pautex et al., 2013; You et al., 2015). In contrast to the study by Hanson et al. (2017) where the video is first watched and then use as basis for discussion, Fact Box could be used in direct communication and their easily understandable language could help physicians, and potentially proxy decision-makers, finding adequate language. Consistent with a prior study demonstrating the appeal of brief decision support tools to physicians,(Giguere et al., 2015) in study 2 all but one physician (29 of 30) stated they would use Fact Boxes as communication tool in practice.

Research has examined the impact of decision-support tools on communication between providers and families at various time points in the medical settings (Einterz et al., 2014; Hanson et al., 2017). Although this outcome measure is fundamental to assess quality, it may not be the only relevant outcome to capture the aspect dynamic of decision-making. The process of decision-making goes beyond the medical setting and really interferes in the life of decision-makers. Research has shown that family decision-makers report having difficulties coping with decision-making, in particular due to discordant opinions of other family members about the ‘right’ decision (Givens et al., 2012; Vig et al., 2007). To date, the

effects of decision support tools on the decision-maker's own dynamic reflections and in relationship to other family members or friends has not been studied in advanced dementia. A study on dyadic coping among couples affected by cancer used audio recorders over one weekend to capture spontaneous conversations and found that cancer was a topic of approximately 5% of the couples' conversations and the spouses' engaged reflections predicted better patient adjustment (Robbins, López, Weihs, & Mehl, 2014). These findings suggest that the topic of chronic disease is part of everyday life conversation among affected families and structured decision aid could presumably enrich these conversations.

Through improving decisional outcomes of a variety of decision-makers, potentially promoting less aggressive care, and providing physicians with a useful communication tool, Fact Boxes can promote high-quality decision-making and thus *healthy ageing* in both decision-makers and patients. Fact Boxes may be used as an information and communication support for goals of care discussions.

6.4. Controversial End-of-Life Practices and Decision-Making

When discussing medical decision-making in advanced dementia a topic certainly worth addressing pertains to decisions about more controversial end-of-life practices such as assisted dying and continuous deep sedation until death.

Individuals *age healthy* when they can *do what they have reason to value* (p. 28; World Health Organization, 2015b). The ability to decide about one's time of death is a source of control and freedom. Assisted dying is thus not just a matter of personal choice but also a potential opportunity for well-being. The fear of an impoverished existence and loss of control over life and death that may result from neurodegenerative diseases such as dementia explain increasing interest for assisted dying among the general population (Kouwenhoven et

al., 2012). It seems to be in some contrast, then, that 77% of physicians 46% of proxies would somewhat disagree or completely disagree with the use of assisted dying if they were responsible for a patient with advanced dementia. These findings corroborate prior research showing a divergence between personal decisions and those that are made on someone else's behalf (Bolt et al., 2015; Kouwenhoven et al., 2015; Tomlinson & Stott, 2014).

Although most proxies may support the idea that patients with advanced dementia have the right to die, they also report the challenging complexity of assisted dying among these patients (Tomlinson et al., 2015). Decision-makers may already face other decisions that imply having accepted the patient's imminent death, such as deciding to forego life-sustaining measures in order to meet the goals of care. In this sense, continuous deep sedation until death may be situated more towards the extreme end of the choice continuum. Although this practice does not hasten death, it does put the patient in an artificial sleep, allowing family members to prepare themselves for the patient's death. Compared to assisted dying, a higher proportion of physicians (52%) agreed with sedation. While assisted dying is relatively more brutal and requires physicians to complete the final act, sedation is more in line with an understanding of death as a natural end-point. Sedation medications solely accompany the dying process without interfering with the natural time point of death in any drastic way.

Advanced directives are substantial as they provide individuals a way to compensate for impaired decisional capacities and thus the opportunity to still *do what they have reason to value* (World Health Organization, 2015b). Because advanced directives inform about the patient's preferences, they also provide significant help and relief for decision-makers when making care decisions on behalf of the patient. In the specific case of advanced euthanasia

directives, however, one chief concern is that preferences change over time,(E. J. Emanuel et al., 2000) and that patients who imagine a future with advanced dementia as one not worth living may still retain a desire to live once they are actually in that state. Given this uncertainty, physicians are often reluctant to take responsibility for a final act that might additionally go against their own values, even in the face of a request in an advanced euthanasia directive that was prepared when the patient's decision-making capacity was still intact (Kouwenhoven et al., 2015). This reveals the delicate challenges of end-of-life decision-making on behalf of someone else: the degree to which decisions can be made in accordance with the patient's preferences is informed by the extent to which they respect values of both the patient *and* decision-maker.

Legalizing assisted dying for patients with advanced dementia does not necessarily make it permissible from the decision-maker's perspective. Despite progress in palliative medicine, there are cases in which there are no alternative choices available that *stabilize functional ability* of the patient with advanced dementia, and choosing death may be the only way to respect the patient's preferences and enable *well-being*. Notably, what may stabilize the functional ability of the decision-maker may not necessarily stabilize the functional ability of the patient, and vice versa. Given that control over the time point of death is a source of freedom and subsequently *well-being* and *healthy ageing* for both parties, adequate information throughout all stages could help synchronize preferences and thus optimize overall outcomes.

6.5. Limitations

This thesis has several limitations that merit discussion. First, the studies were limited to cohorts of participants living in Massachusetts (United States) and the Swiss-German

region of Switzerland. Findings thus may not generalize to other regions. Second, the recruitment process of the DEMFACT study (studies 2 and 3) relied on various organizations such as the Alzheimer Association Zurich, which resulted in lower participation rates (7%) compared to the combined cohorts of study 1 (the SPREAD study, 38%; the EVINCE study, 37%) that recruited from medical institutions (Mitchell et al., 2013; 2014; 2017). Recruitment via medical institutions using multiple recruitment waves should be preferred over one-time recruitment via private organizations. Moreover, participation rates in the DEMFACT study were more than twice as high in physicians (13%) compared to relatives (5%) and professional guardians (6%). This difference may be explained by the specific medical topic as it may have been aversive to proxies without medical expertise who may not have been currently concerned with the topic under study. In this regard, too, recruiting via medical institutions may enable better targeting of the study population while also providing a form of middleman, which helps identify and ensure participation of eligible participants. Based on these considerations, our findings cannot be generalized to eligible non-participants. Third, the questions that were used to assessed proxy predictions of prognosis (study 1) and physicians and proxies perceptions about controversial end-of-life practices (study 3) may not have been detailed enough to capture nuances in respondents' attitudes (Magelssen et al., 2016; Perez-Cruz et al., 2014; N. White et al., 2017). In study 3, for example, participants were asked to ignore the fact that assisted dying in advanced dementia is illegal in Switzerland. An additional question without this caveat would have served to rule out that responses are otherwise anchored on the extant legal framework. However, studies from countries where assisted dying in advanced dementia is permitted found similar proportions in decision-maker's perceptions (Bolt et al., 2015; Rurup et al., 2006). Fourth, the findings presented in this thesis do not speak to the exact factors which may have driven participants'

perception of prognosis (study 1), changes in treatment decisions (study 2), and perceptions about controversial end-of-life practices (study 3). It is likely that some, potentially qualitative, elements not captured in the dataset may have impacted response outcomes. Fifth, despite the important finding that goals of care discussions could play a role in the relationship between proxy perception of prognosis and end-of-life care, the data does not license inferences about the nature of this relationship in terms of the exact attributes of a beneficial goals of care discussion. For instance, we cannot determine the relative impact of content, length, or physicians' communication skills on the relevant outcomes in question. Lastly, statistical power may have been insufficient to detect significant differences in findings that were based on secondary outcomes (e.g., study 3), and future replications should serve to further rule out false positives.

6.6. Research and Clinical Implications

The three studies presented in this thesis have significant implications for research in advanced dementia and palliative care, as well as for clinical practice in terms of care management of patients with advanced dementia. On an even larger scale, implications may extend to the public health system as well. In advancing our understanding of medical decision-making in advanced dementia and promoting less aggressive treatments, these studies are of direct relevance to the WHO global action plan on the public health response to dementia (World Health Organization, 2017).

Study 1 informs research on the development of mortality risk scores for advanced dementia by demonstrating that the accuracy of proxy's prognoses were modest, but remarkably similar to estimates that were based on the empirically derived Advanced Dementia Prognostic Tool (ADEPT; Mitchell, Miller, Teno, Kiely, Davis, & Shaffer, 2010b).

The ADEPT estimates prognosis based on factors such as the patient's demographic, health, history and personality. Regardless of prognostic accuracy, however, the proxy *perception* that the resident may die within 6 months was associated with the use of fewer burdensome interventions. In advanced dementia, highly accurate prognostication may be elusive. However, a general understanding of the terminal nature of this condition may be pertinent to promoting a comfort-focused approach to care (Mitchell, Kiely, & Hamel, 2004a; van der Steen et al., 2013). As suggested by the findings in study 1, goals of care discussions with providers may be important for proxies to gain this understanding. The insight that it may not be the actual life expectancy of the patient but rather the prognosis *perceptions* of proxies that drive end-of-life care decisions is of tremendous value for clinical practice. During counseling, physicians could first establish the proxies' perception of the life expectancy of the patient as a basis for how they subsequently provide prognostic information. This communication strategy could prevent misunderstanding between physicians and proxies (D. B. White et al., 2016a). Lastly, the fact that prognosis estimates of both mortality risk tools and key decision-makers are of limited accuracy is highly relevant for the U.S health care system. For example, patients can only access U.S. Medicare Hospice benefits and thus high-quality palliative care, if they have an estimated life expectancy of 6 months or less (The National Hospice Organization, 1996). Providing access to this service based on the goals of care instead of the estimated life expectancy of a patient may thus be more appropriate.

Study 2 informs research on the development of decision-support tools in advanced dementia and suggests that, compared to more elaborate video decision support tools, simple Fact Boxes may be equally effective, less expensive, handy and thus easier to incorporate into real-life settings. Resources that are currently used to develop and implement more elaborate tools could thus be made available to support other kinds of improvements. Moreover, and

more importantly for the current purposes, study 2 informs research on the development of Fact Boxes for other medical topics (McDowell et al., 2016). Our Fact Boxes for advanced dementia were effective despite the fact that they displayed relatively little evidence compared to previous Fact Boxes that relied on a richer basis of evidence. Because Fact Boxes benefited various decision-makers, research should tailor decision supports to physicians, relatives, but also to professional guardians, as they constitute an understudied population. Given the public health threat of MDROs, the Fact Box on the use of antibiotics in advanced dementia could be a promising tool for reducing the global burden of the spread of MDROs (Ho et al., 2010; World Health Organization, 2014b). If Fact Boxes are found to be also effective in real-life settings, they would be exactly the kind of material that could be shared on the WHO's newly developed global dementia observatory platform (World Health Organization, 2016).

Study 3 informs research on assisted dying and continuous deep sedation in advanced dementia and provides preliminary but novel findings about physicians' and proxies' opinions about the use of these practices. In general, there is a clear need to improve end-of-life care in patients with advanced dementia, but it remains controversial whether such practices could contribute to this goal. While assisted dying is illegal in most countries,(E. J. Emanuel et al., 2016; Li et al., 2017) findings about the relative reluctance of physicians compared to proxies may be interesting for countries that consider extending legalization to patients with advanced dementia. For the Netherlands, Belgium, and Luxembourg, where assisted dying is legal, these findings may suggest that physicians and proxies could benefit from increased ethical guidance and support, respectively (Neil, 2016). Regarding both assisted dying and continuous deep sedation, perceptions were divided and less than half of the decision-makers would support these practices. In the face of likely disagreement

between decision-makers in real-world practice contexts, a shared-decision-making process that is mediated by standardized decision supports might play a substantial role in coordinating medical decision-making.

This thesis has tackled several topics of high priority: dementia, palliative care, medical decision-making, prognosis, risk communication, MDROs, assisted dying, and continuous deep sedation. The management of patients with advanced dementia is a global burden and concern, and the three studies presented here contribute to promoting well-being in both decision-makers and patients affected by dementia. Lastly, this thesis may provide a basis for discussion and reinterpretation of the concept of *Healthy Ageing* in individuals with chronic and terminal illness who are no longer able to make decisions.

6.7. Going Forward

This thesis has provided support for the notion that goals of care discussions and brief decision support tools tailored to various decision-makers are key resources for medical decision-making. Therefore, future contributions should investigate how and when to best use these resources.

The data presented in study 1 did not capture the content of goals of care discussions, rendering the specific factors that impacted proxies' perception about a poor prognosis unclear. Because *perception* of prognosis may drive end-of-life decisions, structured communication support tools that share the advantages of Fact Boxes but focus on proxies' perceptions could be promising. Given the implications outlined above, developing effective, standardized material to guide goals of care discussions to be used in practice is a research priority.

The clinical course of patients with advanced dementia has not been well described in Switzerland, and more data is needed to better understand the needs at the end of life that might be specific to this population. Fact Box decision support tools have been found to be effective in hypothetical situations, and a clinical trial could examine their impact in real-life settings. As discussed in the previous chapter, however, Fact Boxes are not mean to be used in isolation. Rather, decision-support tools should be an integral part of a larger intervention that helps communicate treatment effects in advanced dementia (see for example Hanson et al. 2017). Target populations necessarily include physicians but also nurses, relatives, and professional guardians. Outcomes should be analyzed separately for each population to capture and optimally address corresponding differences. Because decisions in the context of critical and terminal illness affect decision-makers beyond the confined space of observed medical settings, it could prove insightful to assess the effects of Fact Boxes on decision-makers' daily lives and reflections beyond those settings. Future work should examine whether the Fact Box on the use of antibiotics in advanced dementia is a suitable measure to reduce the public health burden of MDROs in Switzerland and other countries.

Of direct relevance to end-of-life decision-making in advanced dementia, study 3 has explored the perceptions of physicians and proxies about assisted dying and continuous deep sedation. Because these findings were based on secondary analyses of the DEMFACT study, a replication study with these variables as primary outcomes could serve to confirm our preliminary findings. As in study 3, such a replication should employ a mixed methods design to elucidate which factors have influenced participants' perceptions about the use of these practices. Furthermore, it would also be of interest to examine how increased guidance and support affect subsequent perceptions.

6.8. Conclusion

From a healthy ageing perspective, patients with advanced dementia who lack decision-making capacities need to rely on the ability of decision-makers to anticipate, recognize and fulfill their end-of-life needs in order to enable *well-being despite* or *with dementia and until death*. In this sense, decision-makers may represent the most important resource for patients with advanced dementia in order to ensure that they can *be and to do what they have reason to value* (p. 28) despite their inability to make decisions (World Health Organization, 2015b). Crucially, however, the corresponding decisions affect not only the well-being of the patient but also that of the decision-maker. Therefore, high-quality medical decision-making in advanced dementia may be characterized by the degree to which it enables *well-being* and in turn *healthy ageing* in both decision-makers and patients.

In this thesis, goals of care discussions and brief Fact Box decision support tools improved medical decision-making in advanced dementia in various decision-makers, and resulted in better outcomes for patients as well. Put briefly, goals of care discussions and Fact Boxes are resources for high-quality decision-making, which positively influence end-of-life care. A future clinical trial could further assess decision-making of residents with advanced dementia in Switzerland by testing the efficacy of Fact Box decision support tools in direct communication during goals of care discussions. With respect to controversial end-of-life practices, decision-makers showed no consensus on whether assisted dying and continuous deep sedation should be seen as valid options in advanced dementia. Future work may elucidate the reasons that underlie these perceptions.

This thesis has examined the concept of *Healthy Ageing* in light of the delicate challenges of end-of-life decision-making: the degree to which decisions can be made in

accordance with the patients' preferences depends in no small part on the perceptions, knowledge, and values of the decision maker. In establishing this intricate interrelation, this thesis touched on many global public health priority topics such as dementia and palliative care and highlighted far-reaching implications for the improvement of medical decision-making and care management in advanced dementia in Switzerland and beyond.

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8. Appendix A

Main Results of Study 1 Presented for Both Study Cohorts Combined, and Each Study Separately

Appendix 1. Association between the Proxy Prognostic Estimates and Risk of Death among Nursing Home Residents with Advanced Dementia Dying in SPREAD (N=362), EVINCE (N=402), and Two Studies Combined (N=764)

Appendix 2. Adjusted Association between the Proxy Being Asked About Goals of Care and the Proxy's Perception that the Resident with Advanced Dementia had Less Than 6 Months to Live in SPREAD (N=362), EVINCE (N=402), and Two Studies Combined (N=764)

Appendix 3. Adjusted Association between the Proxy's Perception that the Resident had Less than 6 Months to Live and Use of Any Burdensome Interventions among Nursing Home Residents with Advanced Dementia in SPREAD (N=362), EVINCE (N=402), and Two Studies Combined (N=764)

Appendix A1. Association between the Proxy Prognostic Estimates and Risk of Death among Nursing Home Residents with Advanced Dementia Dying in SPREAD[a] (N=362), EVINCE[a] (N=402), and Two Studies Combined (N=764)[b]

	Adjusted Hazard Ratio[c] (95% Confidence Interval)				Accuracy of Proxy Prognosis[d]
Study Cohort	< 1 Month	1-6 Months	7-12 Months	Don't Know/Refused	*c* Statistic
Combined	27.53 (15.81, 47.95)	4.61 (3.12, 6.79)	1.91 (1.38, 2.64)	0.92 (0.40, 2.14)	0.67
SPREAD	33.49 (10.26, 109.31)	4.47 (3.13, 6.38)	2.34 (1.55, 3.54)	1.53 (0.62, 3.79)	0.65
EVINCE	24.04 (12.66, 45.63)	4.47 (2.58, 7.73)	1.62 (1.02, 2.57)	0.28 (0.04, 1.99)	0.68

[a]SPREAD = the Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia; EVINCE = the Educational Video to Improve Nursing home Care in End-stage dementia.

[b]The distribution of the proxy prognostic estimates at all proxy interviews (N=2649 interviews) for the combined cohort was: < 1 month, N=30 (1.1%); 1-6 months, N=279 (10.5%); 7-12 months, N=664 (25.1%); > 12 months, N=1553 (58.6%); and don't know/refused, N=123 (4.6%). In SPREAD (N=1236 interviews); < 1 month, N=11 (0.9%); 1-6 months, N=99 (8.0%); 7-12 months, N=269 (21.8%); > 12 months, N=790 (63.9%); and don't know/refused, N=67 (5.4%). In EVINCE (N =1413 interviews); <1 month, N=19 (1.3%); 1-6 months, N=180 (12.7%); 7-12 months, N=395 (28.0%); > 12 months, N=763 (54.0%); and don't know/refused, N=56 (4.0%).

[c]Cox proportional hazards regression examined associations between prognostic estimates at each interview date and the risk of the resident dying given that the resident had survived up until that point. Survival times between 6 and 7 months were rounded up or down. Robust standard errors accounted for clustering at the facility-level.

[d]Generalized version of the c statistic allowing for censored data was calculated as a measure of the model's overall accuracy (range 0.5-1, higher scores indicate greater accuracy).

Appendix A2. Adjusted Association between the Proxy Being Asked About Goals of Care and the Proxy's Perception that the Resident with Advanced Dementia had Less Than 6 Months to Live in SPREAD[a] (N=362), EVINCE[a] (N=402), and Two Studies Combined (N=764)[b]

		No. (%) of Assessment Intervals at Which Proxy Estimated Resident had < 6 Months to Live		
Study Cohort	Total No. (%) of Assessment Intervals at Which Proxies Reported Being Asked About Goals of Care[c]	When Proxies were Asked About Goals of Care	When Proxies were not Asked About Goals of Care	Adjusted Odds Ratio[d] (95% Confidence Interval)
Combined	1126/2526 (44.6)	183 (7.2)	126 (5.0)	1.94 (1.50, 2.52)
SPREAD	525/1169 (44.9)	70 (6.0)	40 (3.4)	2.17 (1.36, 3.46)
EVINCE	601/1357 (44.3)	113 (8.3)	86 (6.3)	1.78 (1.30, 2.44)

[a]SPREAD = the Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia; EVINCE = the Educational Video to Improve Nursing home Care in End-stage dementia.

[b]Proportion of the proxy interviews with prognostic estimates < 6 months; combined cohort, N=309/2526 (12%); SPREAD, N=110/1169 (9.4%); and EVINCE, N=199/1357 (14.7%).

[c]Analyses were at the level of assessment intervals. Resident chart reviews and proxy interviews were done at baseline and quarterly for up to 12 months. Static variables were brought forward from baseline. Proxy's perception of prognosis and other dynamic variables (e.g., goals of care discussion, hospital transfers) were ascertained from each assessment period.

[d]Adjusted odds ratio accounted for clustering among resident/proxy dyads using generalized estimating equations. The model was adjusted for the following variables: resident age (dichotomized at median), resident gender, resident race (white versus other), Alzheimer's versus other dementia type, chronic obstructive pulmonary disease, congestive heart failure, diabetes, Test for Severe Impairment = 0 (versus > 0) (range 0-24, lower scores indicate greater cognitive impairment), Bedford Alzheimer's Nursing Severity-Subscale score > 21 (range 7-28, higher scores indicate more disability), hospital transfer in prior 3 months, proxy age (dichotomized at median), proxy gender, and proxy relationship to resident.

Appendix A3. Adjusted Association between the Proxy's Perception that the Resident had Less than 6 Months to Live and Use of Any Burdensome Interventions[a] among Nursing Home Residents with Advanced Dementia in SPREAD[b] (N=362), EVINCE[b] (N=402), and Two Studies Combined (N=764)[c]

Study Cohort	Total No. (%) of Assessment Intervals in Which Proxy Estimated Resident Prognosis < 6 Months[d]	No. (%) of Assessment Intervals in Which Resident had Any Burdensome Interventions		Adjusted Odds Ratio[e] (95% Confidence Interval)
		When Proxy Estimated Prognosis < 6 Months	When Proxy Estimated Prognosis > 6 Months	
Combined	251/2031 (12.4)	89 (4.4)	1008 (49.6)	0.46 (0.34, 0.62)
SPREAD	87/928 (9.4)	38 (4.1)	480 (51.7)	0.60 (0.35, 1.02)
EVINCE	164/1103 (14.9)	51 (4.6)	528 (47.9)	0.40 (0.27, 0.57)

[a]Burdensome interventions included any of the following: hospital transfer (hospitalization or emergency room visits), parenteral therapy, new feeding tube insertion, venipuncture and bladder catheterizations.

[b]SPREAD = the Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia; EVINCE = the Educational Video to Improve Nursing home Care in End-stage dementia.

[c]In the combined cohort at all resident-assessment intervals (i.e., baseline and follow-up; N=2031) the proportion of intervals during which residents experienced at least one burdensome intervention was: combined cohort, N=1097/2037 (54.0%); SPREAD, N=518/928 (55.8%); and EVINCE, N=579/1103 (52.5%).

[d]Analyses were at the level of assessment intervals. Resident chart reviews and proxy interviews were done at baseline and quarterly for up to 12 months. Proxy prognosis was taken from the interview done at the start of the interval. The use of burdensome interventions reflects the residents experience during the 3-month interval following that interview.

[e] Adjusted odds ratio accounted for clustering among resident/proxy dyads using generalized estimating equations. The model was adjusted for the following variables: resident age (dichotomized at median), resident gender, resident race (white versus other), Alzheimer's versus other dementia type, chronic obstructive pulmonary disease, congestive heart failure, diabetes, Test for Severe Impairment = 0 (versus > 0) (range 0-24, lower scores indicate greater cognitive impairment), Bedford Alzheimer's Nursing Severity-Subscale score > 21 (range 7-28, higher scores indicate more disability), any new major illness in prior 3 months, proxy age (dichotomized at median), proxy gender, proxy relationship to resident, and goals of care discussions.

9. Appendix B

Supplementary Material of Study 2

Appendix 1. Fact Box Decision Support Tool: Antibiotics For Pneumonia in Advanced Dementia

Appendix 2. Fact Box Decision Support Tool: Artificial Hydration in Advanced Dementia

Appendix 3. Knowledge Scale About the Use of Antibiotics for Pneumonia in Advanced Dementia

Appendix 4. Knowledge Scale About the Use of Artificial Hydration in Advanced Dementia

Appendix 5. The CONSORT flow diagram of participant subgroups

Appendix 6. Distribution of Missing Values in Decisional Conflict Scores by Trial Arm, and for Each Participant Subgroup Separately

Appendix 7. Distribution of Missing Values in Knowledge Scores and Preferences to Forego Antibiotics and Artificial Hydration by Trial Arm, and for Each Participant Subgroup Separately

Appendix B1. Fact Box Decision Support Tool: Antibiotics For Pneumonia in Advanced Dementia

The best available scientific information regarding the benefits and harms of antibiotics for pneumonia in patients with advanced dementia comes from observational studies[1]. The findings represented here refer to patients with advanced dementia (aged 58 years and above) who were diagnosed with lower respiratory infection or pneumonia. Patients either received antibiotics or no antibiotic.

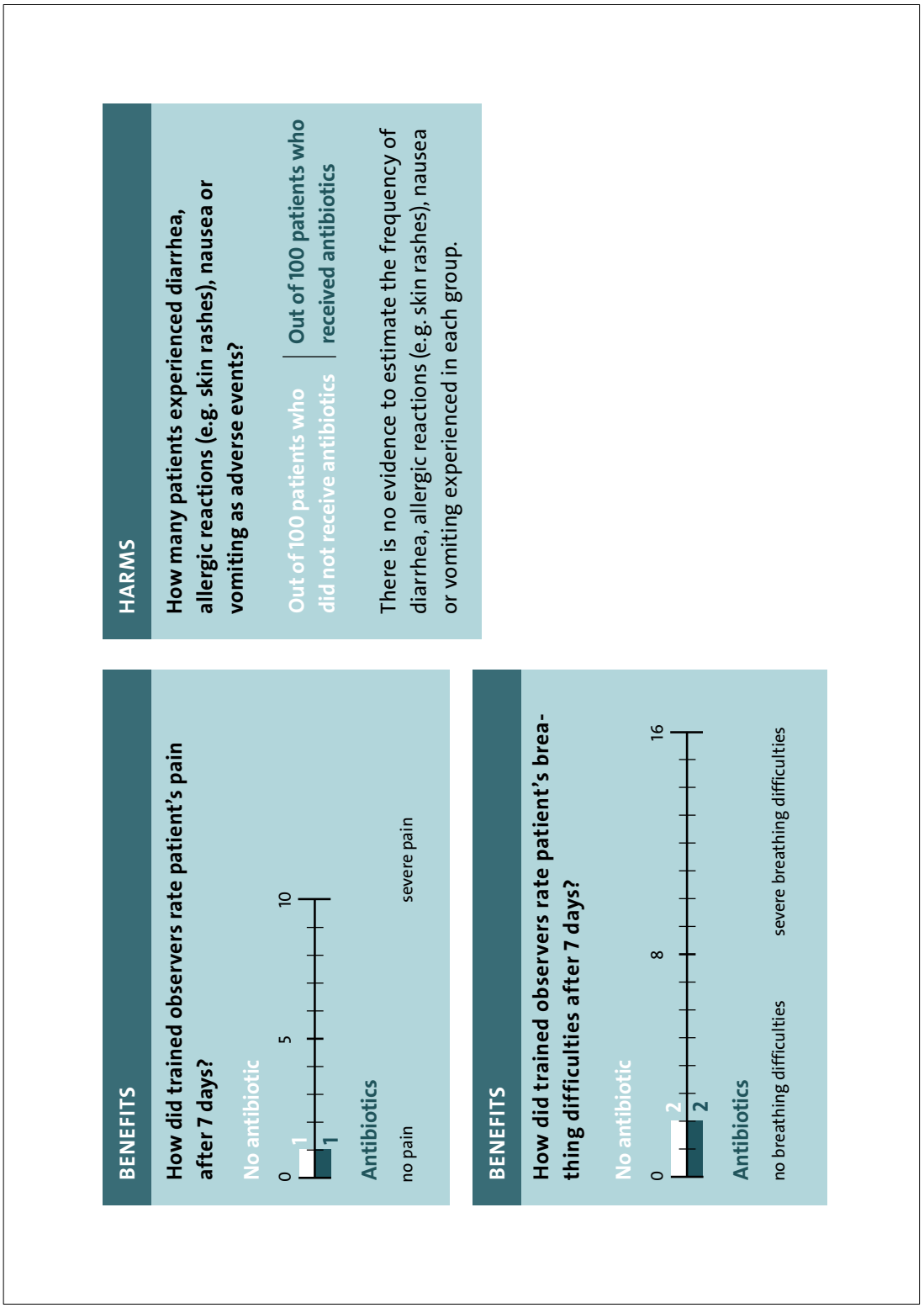
[1] Observational studies observe outcomes in people who opt for different treatments. These studies cannot establish whether an outcome is caused by the treatment or by some other causes.

BENEFITS

How many patients died within 1 month?

Out of 100 patients who did not receive antibiotics	Out of 100 patients who received antibiotics

Pneumonia can lead to higher mortality in patients with advanced dementia, independently of whether patients received antibiotics or not. There are insufficient good quality studies to estimate how many patients with advanced dementia die in each group. One study found that fewer people with advanced dementia died within ten days of starting antibiotic treatment compared to patients who did not receive antibiotics. However, there was no meaningful difference between groups after a one-month observational period.


BENEFITS
How did trained observers rate patient's pain after 7 days?
No antibiotic
0
1
5
10
1
Antibiotics
no pain
severe pain
BENEFITS
How did trained observers rate patient's breathing difficulties after 7 days?
No antibiotic
0
2
8
16
2
Antibiotics
no breathing difficulties
severe breathing difficulties
HARMS
How many patients experienced diarrhea, allergic reactions (e.g. skin rashes), nausea or vomiting as adverse events?
Out of 100 patients who did not receive antibiotics
Out of 100 patients who received antibiotics
There is no evidence to estimate the frequency of diarrhea, allergic reactions (e.g. skin rashes), nausea or vomiting experienced in each group.

ARE THERE ALTERNATIVES TO ANTIBIOTICS?

In order to control symptoms of discomfort, therapies other than antibiotics may be considered. These include medications to control pain and breathing difficulties (e.g. opioids), oxygen (usually given via face mask), as well as sedative medication to reduce anxiety.

SUMMARY

There are insufficient good quality studies on the efficacy of antibiotics for pneumonia in patients with advanced dementia. Pneumonia is associated with an increased risk of mortality in this population, independently of whether or not antibiotics are administered. One study found that antibiotics may decrease mortality in the short term but this difference is not maintained over the longer term. Patients with advanced dementia experienced a relatively low level of pain and breathing difficulties that does not differ between groups. Antibiotics may cause adverse events, however exact numbers are not known.

Last update 28.6.2016

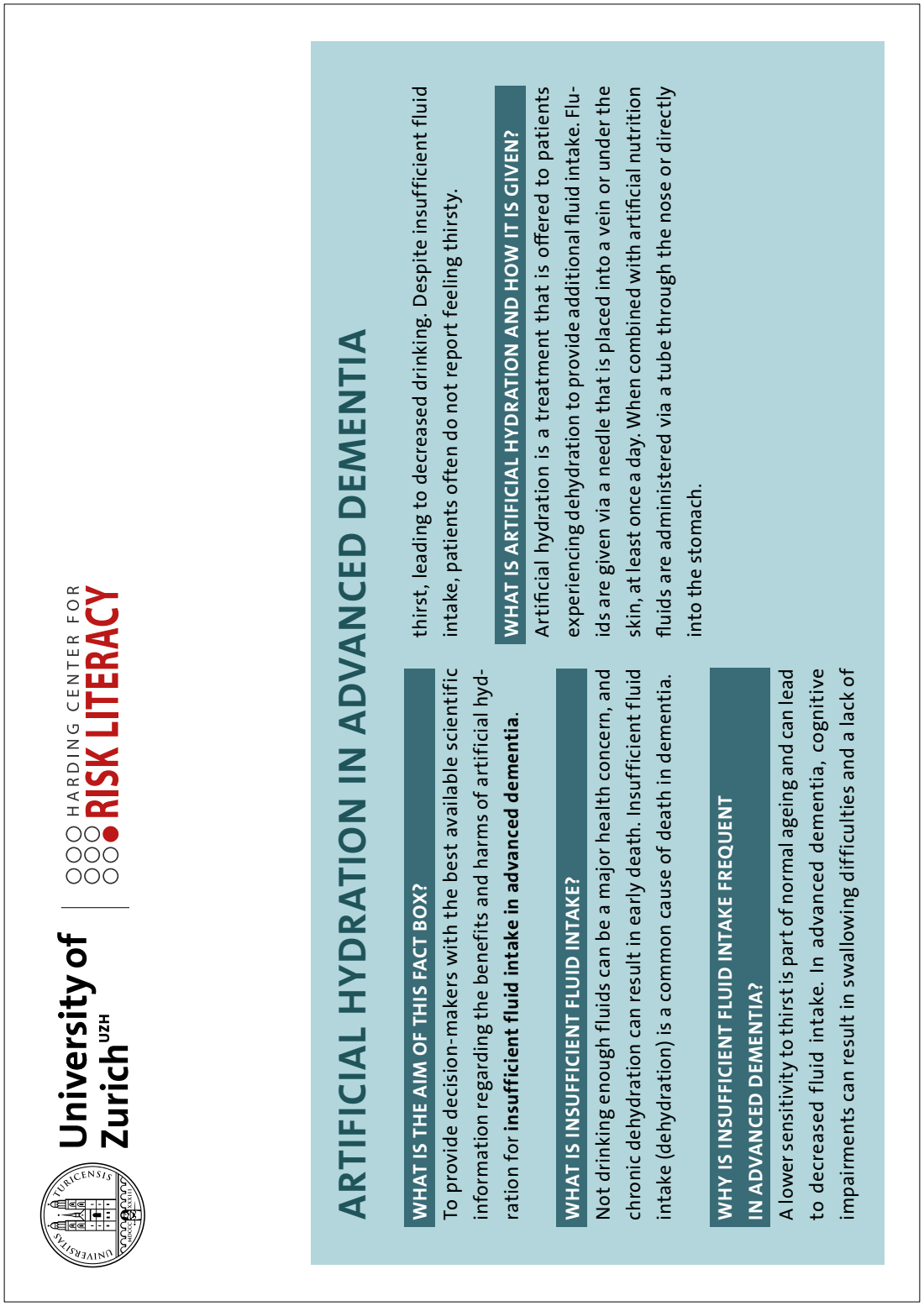
SOURCES

van der Steen et al., (2012). ***JAMDA***
doi.org/10.1016/j.jamda.2010.07.001
van der Maaden et al., (2016). ***JAMDA***
doi.org/10.1016/j.jamda.2015.08.010, unpublished data

This fact box was developed by the Center for Gerontology Zurich of the University of Zurich and the Division of Psychiatry Research and Psychogeriatric Medicine of the University of Zurich, Switzerland, in collaboration with the Harding Center For Risk Literacy of the Max Planck Institute for Human Development, Berlin, Germany.

Sponsored by the Swiss Academy of Medical Sciences (SAMS), Stanley Thomas Johnson Foundation, and the Gottfried and Julia Bangerter-Rhyner-Foundation

Appendix B2. Fact Box Decision Support Tool: Artificial Hydration in Advanced Dementia



The best available scientific information regarding the benefits and harms of artificial hydration for insufficient fluid intake in patients with advanced dementia comes form observational studies[1], or studies on other patient groups (e.g. patients with advanced *cancer*). The findings represented here refer to patients with advanced dementia (average age 85) who had insufficient fluid intake. Patients either received artificial hydration or no artificial hydration.

[1] Observational studies observe outcomes in people who opt for different treatments. These studies cannot establish whether an outcome is caused by the treatment or by some other causes.

BENEFITS

How many patients died within 6 weeks?

Out of 100 patients who did not receive artificial hydration	Out of 100 patients who received artificial hydration

There are insufficient good quality studies to estimate how many patients with advanced dementia die in each group. One study found that many patients with advanced dementia who did not receive artificial hydration died within a few weeks. However, one better quality study on patients with advanced *cancer* who experienced dehydration found no meaningful difference between the numbers of patients who died in each group.

BENEFITS

How many patients experienced pain?

Out of 100 patients who did not receive artificial hydration	Out of 100 patients who received artificial hydration

There are insufficient good quality studies to estimate how many patients with advanced dementia experience pain in each group. In a study on advanced *cancer* patients who experienced dehydration, there was no meaningful difference on the amount of pain between the groups after seven days.

HARMS

How many patients experienced an unnatural fluid accumulation as an adverse event?

Out of 100 patients who did not receive artificial hydration	Out of 100 patients who received artificial hydration

Artificial hydration may lead to an abnormal accumulation of fluid around the lung (pulmonary oedema) or the limb (e. g. swollen legs). There is no evidence to estimate the frequency of unnatural fluid accumulations experienced in each group.

How many patients experienced infections at the injection site as an adverse event?

Out of 100 patients who did not receive artificial hydration	Out of 100 patients who received artificial hydration

The placement of the needle may result in discomfort, local infections, bleeding or swelling at the injection site. There is no evidence to estimate the frequency of infections at the injection site experienced in each group.

ARE THERE ALTERNATIVES TO ARTIFICIAL HYDRATION?

In order to control symptoms of discomfort, therapies other than artificial hydration may be considered. These include medications to reduce pain and anxiety, as well as mouth care. A dry mouth can cause thirst and can be treated with good mouth care.

SUMMARY

There are insufficient good quality studies on the efficacy of artificial hydration for insufficient fluid intake in patients with advanced dementia. Dehydration is associated with an increased risk of mortality in this population, independently of whether or not artificial hydration is provided. One good quality study on advanced *cancer* patients with dehydration found no benefit on mortality and no difference in the level of pain between groups. Artificial hydration may cause adverse events, however exact numbers are not known.

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This fact box was developed by the Center for Gerontology Zurich of the University of Zurich and the Division of Psychiatry Research and Psychogeriatric Medicine of the University of Zurich, Switzerland, in collaboration with the Harding Center For Risk Literacy of the Max Planck Institute for Human Development, Berlin, Germany.

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Appendix B3. Knowledge Scale About the Use of Antibiotics for Pneumonia in Advanced Dementia

The DemFACT trial ascertained participant's knowledge about the use of antibiotics for pneumonia in advanced dementia using a 7-item true-false scale in German (scored, 1=true, 0=false/don't know; range 0-7, higher scores indicate greater knowledge). For the purpose of this report the scale has been translated into English (see next page).

Original German Version:

In diesem Teil möchten wir gerne wissen, was Sie über Antibiotika gegen Lungenentzündung bei fortgeschrittener Demenz wissen. Versuchen Sie die Fragen so gut wie möglich zu beantworten.
Was wissen Sie über den Einsatz von Antibiotika bei Patienten/innen mit fortgeschrittener Demenz und Lungenentzündung?

		Richtig	Falsch	Weiss nicht
A	**Nutzen von Antibiotika gegen Lungenentzündung bei fortgeschrittener Demenz**			
a	Antibiotika können das Leben um ein paar Tage, jedoch nicht um mehr als einen Monat, verlängern.	☐	☐	☐
b	Die Gabe von Antibiotika erleichtert Atembeschwerden stärker, als wenn keine Antibiotika verabreicht werden.	☐	☐	☐
c	Die Gabe von Antibiotika lindert Schmerzen stärker, als wenn keine Antibiotika verabreicht werden.	☐	☐	☐
d	Antibiotika bei einer Lungenentzündung können das Leben um mehr als einen Monat verlängern.	☐	☐	☐
B	**Risiken von Antibiotika gegen Lungenentzündung bei fortgeschrittener Demenz**			
a	Antibiotika haben keine bedeutsamen Nebenwirkungen.	☐	☐	☐
b	Durchfall, allergische Reaktionen (z.B. Hautausschläge), Übelkeit oder Erbrechen sind Nebenwirkungen von Antibiotika.	☐	☐	☐
c	Blutdruckanstieg, Gewichtszunahme oder Osteoporose sind Nebenwirkungen von Antibiotika.	☐	☐	☐

English translation:

In this section, we are interested in your knowledge about the use of antibiotics for pneumonia in advanced dementia. Try to answer the questions as best you can.

What do you know about the administration of antibiotics for patients with advanced dementia and pneumonia?

		N=Correct / N=Total (%)[a]	
		Intervention, N=114	Control, N=118
A	**Benefits of Antibiotics for Pneumonia in Advanced Dementia**		
a	Antibiotics can prolong life by a couple of days, but not by more than one month.	70/112 (62.5)	15/118 (12.7)
b	The administration of antibiotics relieves breathing difficulties more than if no antibiotics are administered.	84/112 (75.0)	34/117 (29.1)
c	The administration of antibiotics alleviates pain more than if no antibiotics are administered.	89/112 (79.5)	43/118 (36.4)
d	Antibiotics for pneumonia can prolong life by more than one month.	86/112 (76.8)	19/118 (16.1)
B	**Harms of Antibiotics for Pneumonia in Advanced Dementia**		
a	Antibiotics cannot cause significant adverse events.	98/111 (88.3)	97/117 (82.9)
b	Diarrhea, allergic reactions (e.g., skin rashes), nausea or vomiting are adverse events of antibiotics.	88/111 (79.3)	93/118 (78.8)
c	Hypertension, weight gain, or osteoporosis are adverse events of antibiotics.	80/112 (71.4)	50/118 (42.4)

[a]*Number of correct responses (versus number of wrong or don't know responses) by total number of observations per item were taken from the one-month follow-up assessment for the intervention and control arms.*

Appendix B4. Knowledge Scale About the Use of Artificial Hydration in Advanced Dementia

The DemFACT trial ascertained participant's knowledge about the use of artificial hydration in advanced dementia using a 7-item true-false scale in German (scored, 1=true, 0=false/don't know; range 0-7, higher scores indicate greater knowledge). For the purpose of this report the scale has been translated into English (see next page).

Original German Version:

In diesem Teil möchten wir gerne wissen, was Sie über künstliche Flüssigkeitszufuhr bei fortgeschrittener Demenz wissen. Versuchen Sie die Fragen so gut wie möglich zu beantworten.
Was wissen Sie über den Einsatz von künstlicher Flüssigkeitszufuhr bei Patienten/innen mit fortgeschrittener Demenz und Flüssigkeitsmangel (Dehydration)?

		Richtig	Falsch	Weiss nicht
A	**Nutzen von künstlicher Flüssigkeitszufuhr bei fortgeschrittener Demenz (oder *Krebserkrankung*)**			
a	Es gibt nicht genügend Daten über die Wirkung von Künstlicher Flüssigkeitszufuhr auf die Sterblichkeit von Patienten/innen mit einer fortgeschrittenen Demenz.	☐	☐	☐
b	Es gibt nicht genügend Daten über die Wirkungen von künstlicher Flüssigkeitszufuhr auf die Schmerzen der Patienten/innen mit fortgeschrittener Demenz.	☐	☐	☐
c	Künstliche Flüssigkeitszufuhr kann bei Patienten/innen mit einer fortgeschrittenen *Krebserkrankung* das Leben um einige Tage, jedoch nicht um mehr als einen Monat, verlängern.	☐	☐	☐
d	Künstliche Flüssigkeitszufuhr lindert bei Patienten/innen mit einer fortgeschrittenen Krebserkrankung die Schmerzen stärker, als wenn keine künstliche Flüssigkeitszufuhr veranlasst wird.	☐	☐	☐
B	**Risiken von künstlicher Flüssigkeitszufuhr bei fortgeschrittener Demenz**			
a	Künstliche Flüssigkeitszufuhr hat keine bedeutsamen Nebenwirkungen.	☐	☐	☐
b	Unnatürliche Ansammlung von Flüssigkeit im Bereich der Lunge (Lungenödem) oder in den Beinen sind Nebenwirkungen von künstlicher Flüssigkeitszufuhr.	☐	☐	☐
c	Entzündungen am venösen Zugang (Einstichort) sind Nebenwirkungen von künstlicher Flüssigkeitszufuhr.	☐	☐	☐

English translation:

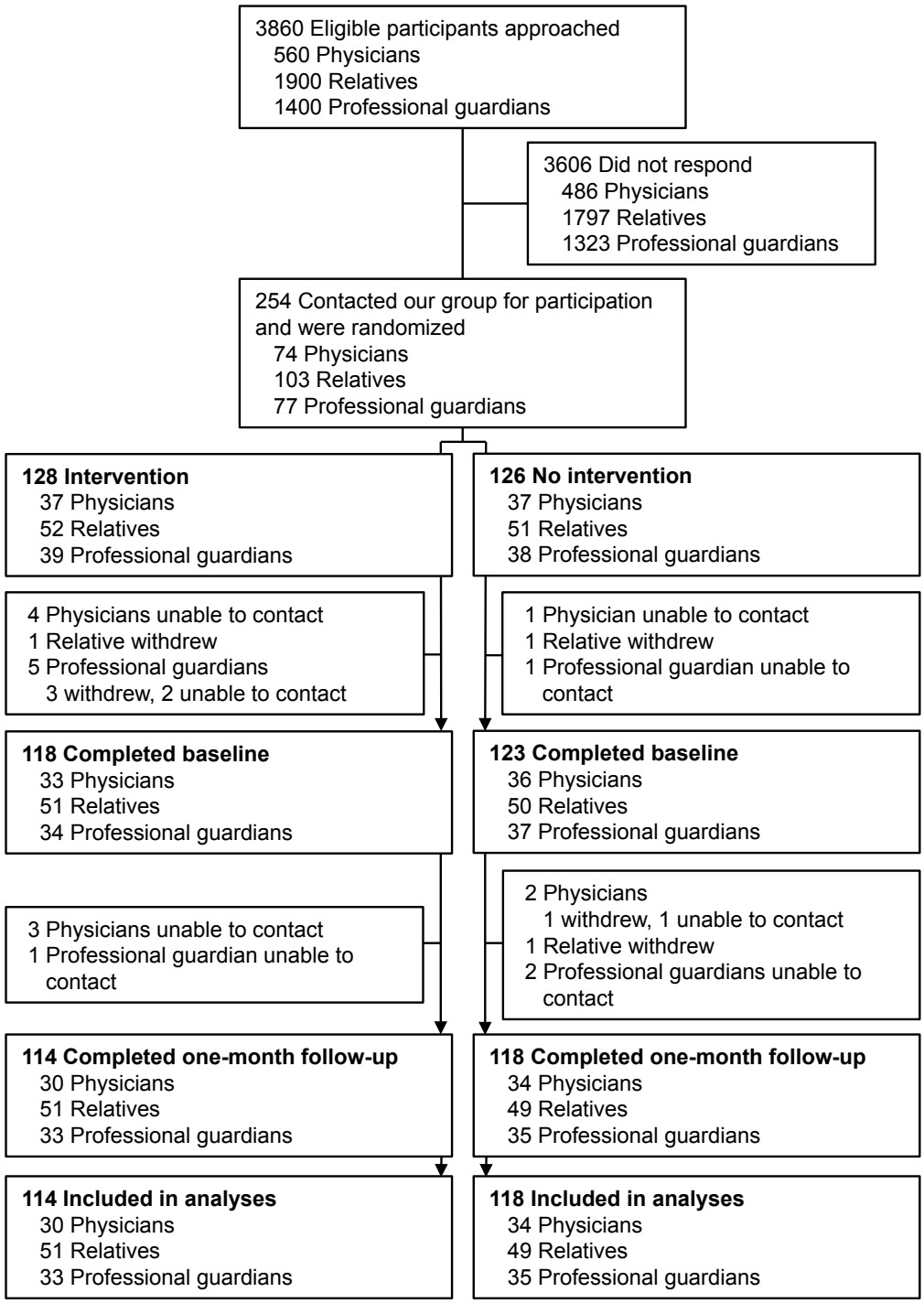
In this section, we are interested in your knowledge about the use of artificial hydration in advanced dementia. Try to answer the questions as best you can.

What do you know about the administration of artificial hydration for patients with advanced dementia and suspected insufficient fluid intake (dehydration)?

		N=Correct / N=Total (%)[a]	
		Intervention, N=114	Control, N=118
A	**Benefits of Artificial Hydration in Advanced Dementia (or *Advanced Cancer*)**		
a	There are insufficient data about the effects of artificial hydration on survival of patients with advanced dementia.	106/113 (93.8)	26/117 (22.2)
b	There are insufficient data about the effects of artificial hydration on the pain experienced by patients with advanced dementia.	105/114 (92.1)	29/118 (24.6)
c	Artificial hydration can prolong the life of patients with *advanced cancer* by a couple of days, but not by more than one month.	50/113 (44.2)	20/118 (16.9)
d	Artificial hydration alleviates the pain experienced by patients with *advanced cancer* more than if no artificial hydration is administered.	91/111 (82.0)	53/118 (44.9)
B	**Harms of Artificial Hydration in Advanced Dementia**		
a	Artificial hydration cannot cause significant adverse events.	96/113 (85.0)	65/117 (55.6)
b	Abnormal accumulation of fluid in the lungs (pulmonary oedema) or legs are adverse events of artificial hydration.	106/114 (93.0)	60/118 (50.9)
c	Local infections at the injection site (the venous access where the needle is placed) are adverse events of artificial hydration.	105/114 (92.1)	78/118 (66.1)

[a]*Number of correct responses (versus number of wrong or don't know responses) by total number of observations per item were taken from the one-month follow-up assessment for the intervention and control arms.*

Appendix B5. CONSORT flow diagram of participant subgroups. The total number of eligible physicians, relatives of dementia patients, and professional guardians who were approached are approximations provided by the organizations that helped with recruitment.



Appendix B6. Distribution of Missing Values in Decisional Conflict Scores by Trial Arm, and for Each Participant Subgroup Separately

	Baseline *No. Missing/No. Total, (%)*		1 Month *No. Missing/No. Total, (%)*	
Participants	Intervention	Control	Intervention, Review Fact Box	Control
All, N=232				
Decisional conflict about				
Antibiotic use	8/114 (7.0)	5/118 (4.2)	6/114 (5.3)	4/118 (3.4)
Artificial hydration use	10/114 (8.8)	7/118 (5.9)	8/114 (7.0)	6/118 (5.1)
Physicians, N=64				
Decisional conflict about				
Antibiotic use	-	-	1/30 (3.3)	1/34 (2.9)
Artificial hydration use	1/30 (3.3)	-	3/30 (10.0)	-
Relatives, N=100				
Decisional conflict about				
Antibiotic use	6/51 (11.8)	3/49 (6.1)	3/51 (5.9)	1/49 (2.0)
Artificial hydration use	8/51 (15.7)	5/49 (10.2)	3/51 (5.9)	4/49 (8.2)
Professional Guardians, N=68				
Decisional conflict about				
Antibiotic use	2/33 (6.1)	2/35 (5.7)	2/33 (6.1)	2/35 (5.7)
Artificial hydration use	1/33 (3.0)	2/35 (5.7)	2/33 (6.1)	2/35 (5.7)

Appendix B7. Distribution of Missing Values in Knowledge Scores and Preferences to Forego Antibiotics and Artificial Hydration by Trial Arm, and for Each Participant Subgroup Separately

	Baseline *No. Missing/No. Total, (%)*		1 Month *No. Missing/No. Total, (%)*	
Participants	Intervention	Control	Interventio, Review Fact Box	Control
All, N=232				
Knowledge about				
Antibiotics use	4/114 (3.5)	6/118 (5.1)	3/114 (2.6)	2/118 (1.7)
Artificial hydration use	3/114 (2.6)	3/118 (2.5)	4/114 (3.5)	2/118 (1.7)
Preferences to forego				
Antibiotic use	1/114 (0.9)	2/118 (1.7)	1/114 (0.9)	-
Artificial hydration use	-	1/118 (0.8)	1/114 (0.9)	-
Physicians, N=64				
Knowledge about				
Antibiotic use	-	2/34 (5.9)	-	1/34 (2.9)
Artificial hydration use	1/30 (3.3)	-	1/30 (3.3)	1/34 (2.9)
Preferences to forego				
Antibiotic use	-	-	-	-
Artificial hydration use	-	-	-	-
Relatives, N=100				
Knowledge about				
Antibiotic use	4/51 (7.8)	2/49 (4.1)	3/51 (5.9)	-
Artificial hydration use	1/51 (2.0)	2/49 (4.1)	2/51 (3.9)	1/49 (2.0)
Preferences to forego				
Antibiotic use	-	1/49 (2.0)	1/51 (2.0)	-
Artificial hydration use	-	-	1/51 (2.0)	-
Professional Guardians, N=68				
Knowledge about				
Antibiotic use	-	2/35 (5.7)	-	1/35 (2.9)
Artificial hydration use	1/33 (3.0)	1/35 (2.9)	1/33 (3.0)	-
Preferences to forego				
Antibiotic use	1/33 (3.0)	1/35 (2.9)	-	-
Artificial hydration use	-	1/35 (2.9)	-	-

10. Curriculum Vitae

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2015 - present	Doctoral Candidate, Department of Psychology, Center for Gerontology, University of Zurich, Switzerland (3rd year as visiting student, Institute for Aging Research, Harvard Medical School Affiliate, Massachusetts, United States)
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